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2nd REVISED NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Publication:	**September 7, 2017**
Date and Time of Meeting:	**Thursday, September 28, 2017 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**
Place of Meeting:	**Springs Preserve** **333 S. Valley View Blvd** **Las Vegas, Nevada 89107**
Place of Meeting:	**Division of Public & Behavioral Health** **4150 Technology Way, Room 301** **Carson City, Nevada 89706** **Please check with staff to verify room location**
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e698cdc3c4cbcc31d4c379331a1f8cebe **OR** www.webex.com, select "Join," enter Meeting Number 644 525 531, your name and email and then select, "Join." A Password should not be necessary, but if asked, enter "9MMZuC88." **OR**

Audio Only: **(763) 957-6300**

Event Number: **644 525 531**

Follow the instructions that appear on your screen to join the teleconference. Audio will also be broadcast over the internet (VoIP).

1. Call to Order and Roll Call

2. Public Comment

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from March 23, 2017

b. Status Update by the DHCFP
   1. Public Comment

4. Annual Review - Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. Analgesics – Opiate Agonists

   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the DHCFP
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Anti-infective Agents – Antivirals – Influenza Agents

   1. Public Comment
   2. Drug Class Review Presentation – OptumRx
   3. **For Possible Action**: Committee Discussion and Action
      a. Approve Clinical/Therapeutic Equivalency of Agents in Class
      b. Identify Exclusions/Exceptions for Certain Patient Groups
   4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
   5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Anti-infective Agents – Quinolones – Quinolones – 3rd Generation

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

d. Autonomic Agents – Sympathomimetics – Self-Injectable Epinephrine

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

e. Biologic Response Modifiers – Immunomodulators – Targeted Immunomodulators

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

f. Biologic Response Modifiers – Multiple Sclerosis Agents – Injectable

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

g. Cardiovascular Agents – Antilipemics – Cholesterol Absorption Inhibitors

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

h. Cardiovascular Agents – Antilipemics – HMG-CoA Reductase Inhibitors (Statins)

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

i. Dermatological Agents – Antipsoriatic Agents – Topical Vitamin D Analogs

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

j. Dermatological Agents – Topical Anti-infectives – Topical Antivirals

1. Public Comment

2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

k. Dermatological Agents – Topical Anti-infectives – Topical Scabicides

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

l. Gastrointestinal Agents – Antiulcer Agents – Proton Pump Inhibitors (PPIs)

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

m. Gastrointestinal Agents – Gastrointestinal Anti-inflammatory Agents

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

n. Hematological Agents – Anticoagulants – Injectable

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

o. Hormones and Hormone Modifiers – Antidiabetic Agents – Biguanides

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

p. Hormones and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

q. Hormones and Hormone Modifiers – Antidiabetic Agents – Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

r. Musculoskeletal Agents – Bone Resorption Inhibitors – Bisphosphonates

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

s. Neurological Agents – Anti-Migraine Agents – Serotonin-Receptor Agonists

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

t. Ophthalmic Agents – Ophthalmic Anti-infectives – Ophthalmic Quinolones

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

u. Psychotropic Agents – ADHD Agents

1. Public Comment

2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

v. Psychotropic Agents – Antipsychotics – Atypical Antipsychotics – Oral

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

w. Respiratory Agents – Respiratory Anti-inflammatory Agents – Leukotriene Receptor Antagonists

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

x. Respiratory Agents – Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP

5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

5. Annual Review – Established Drug Classes

a. Cardiovascular Agents – Antihypertensive Agents – Angiotensin II Receptor Antagonists

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

b. Cardiovascular Agents – Antihypertensive Agents – Calcium-Channel Blockers

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

c. Cardiovascular Agents – Antihypertensive Agents – Vasodilators – Oral

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

d. Gastrointestinal Agents – Antiemetics – Miscellaneous

1. Public Comment

2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

e. Hematological Agents – Anticoagulants – Oral

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

f. Hematological Agents – Platelet Inhibitors Public Comment

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

g. Hormones and Hormone Modifiers – Pituitary Hormones – Growth hormone modifiers

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP

5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

h. Neurological Agents – Anticonvulsants

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

i. Ophthalmic Agents – Ophthalmic Anti-infective/Anti-inflammatory Combinations

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

j. Psychotropic Agents – Anxiolytics, Sedatives and Hypnotics

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

k. Respiratory Agents – Nasal Antihistamines

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action

a. Approve Clinical/Therapeutic Equivalency of Agents in Class
b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

l. Respiratory Agents – Respiratory Anti-inflammatory Agents – Nasal Corticosteroids

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

6. Annual Review – Drug Classes Without Proposed Changes

a. Public Comment
b. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the division of Health Care Financing and Policy Without Changes
   1. Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia Agents
   2. Analgesics - Analgesic/Miscellaneous - Tramadol and Related Drugs
   3. Analgesics - Opiate Agonists - Abuse Deterrent
   4. Analgesics - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral
   5. Antihistamines - H1 blockers - Non-Sedating H1 Blockers
   6. Anti-infective Agents - Antivirals - Alpha Interferons
   7. Anti-infective Agents - Antivirals - Anti-hepatitis Agents - Polymerase Inhibitors/Combination Products
   8. Anti-infective Agents - Antivirals - Anti-hepatitis Agents - Ribavirins
   9. Anti-infective Agents - Antivirals - Anti-Herpetic Agents
   10. Anti-infective Agents - Cephalosporins - Second-Generation Cephalosporins
   11. Anti-infective Agents - Cephalosporins - Third-Generation Cephalosporins
   12. Anti-infective Agents - Macrolides
   13. Anti-infective Agents - Quinolones - Quinolones - 2nd Generation
   14. Biologic Response Modifiers - Multiple Sclerosis Agents - Oral
   15. Biologic Response Modifiers - Multiple Sclerosis Agents - Specific Symptomatic Treatment
   16. Cardiovascular Agents - Antihypertensive Agents - Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
   17. Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers
   18. Cardiovascular Agents - Antihypertensive Agents - Direct Renin Inhibitors

19. Cardiovascular Agents - Antihypertensive Agents - Vasodilators - Inhaled
20. Cardiovascular Agents - Antilipemics - Bile Acid Sequestrants
21. Cardiovascular Agents - Antilipemics - Fibric Acid Derivatives
22. Cardiovascular Agents - Antilipemics - Niacin Agents
23. Cardiovascular Agents - Antilipemics - Omega-3 Fatty Acids
24. Dermatological Agents - Topical Analgesics
25. Dermatological Agents - Topical Anti-infectives - Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products
26. Dermatological Agents - Topical Anti-infectives - Impetigo Agents: Topical
27. Dermatological Agents - Topical Anti-infectives - Topical Antifungals (onychomycosis)
28. Dermatological Agents - Topical Anti-inflammatory Agents - Immunomodulators: Topical
29. Dermatological Agents - Topical Antineoplastics - Topical Retinoids
30. Electrolytic and Renal Agents - Phosphate Binding Agents
31. Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/Combo
32. Gastrointestinal Agents - Antiulcer Agents - H2 blockers
33. Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs (New)
34. Gastrointestinal Agents - Gastrointestinal Enzymes
35. Genitourinary Agents - Benign Prostatic Hyperplasia (BPH) Agents - 5-Alpha Reductase Inhibitors
36. Genitourinary Agents - Benign Prostatic Hyperplasia (BPH) Agents - Alpha-Blockers
37. Genitourinary Agents - Bladder Antispasmodics
38. Hematological Agents - Erythropoiesis-Stimulating Agents
39. Hormones and Hormone Modifiers - Androgens
40. Hormones and Hormone Modifiers - Antidiabetic Agents - Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.
41. Hormones and Hormone Modifiers - Antidiabetic Agents - Dipeptidyl Peptidase-4 Inhibitors
42. Hormones and Hormone Modifiers - Antidiabetic Agents - Insulins (Vials, Pens and Inhaled)
43. Hormones and Hormone Modifiers - Antidiabetic Agents - Meglitinides
44. Hormones and Hormone Modifiers - Antidiabetic Agents - Sulfonylureas
45. Hormones and Hormone Modifiers - Antidiabetic Agents - Thiazolidinediones
46. Hormones and Hormone Modifiers - Progestins for Cachexia
47. Musculoskeletal Agents - Antigout Agents
48. Musculoskeletal Agents - Bone Resorption Inhibitors - Nasal Calcitonins
49. Musculoskeletal Agents - Restless Leg Syndrome Agents
50. Musculoskeletal Agents - Skeletal Muscle Relaxants
51. Neurological Agents - Alzheimers Agents
52. Neurological Agents - Anticonvulsants - Barbiturates
53. Neurological Agents - Anticonvulsants - Benzodiazepines
54. Neurological Agents - Anticonvulsants - Hydantoins
55. Neurological Agents - Antiparkinsonian Agents - Non-ergot Dopamine Agonists
56. Ophthalmic Agents - Antiglaucoma Agents - Carbonic Anhydrase Inhibitors/Beta-Blockers

57. Ophthalmic Agents - Antiglaucoma Agents - Ophthalmic Prostaglandins
58. Ophthalmic Agents - Ophthalmic Antihistamines
59. Ophthalmic Agents - Ophthalmic Anti-infectives - Ophthalmic Macrolides
60. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Corticosteroids
61. Ophthalmic Agents - Ophthalmic Anti-inflammatory Agents - Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
62. Ophthalmic Agents - Ophthalmics for Dry Eye Disease
63. Otic Agents - Otic Anti-infectives - Otic Quinolones
64. Psychotropic Agents - Antidepressants - Other
65. Psychotropic Agents - Antidepressants - Selective Serotonin Reuptake Inhibitors (SSRIs)
66. Psychotropic Agents - Psychostimulants - Narcolepsy Agents
67. Respiratory Agents - Respiratory Anti-inflammatory Agents - Respiratory Corticosteroids
68. Respiratory Agents - Respiratory Anti-inflammatory Agents - Phosphodiesterase Type 4 Inhibitors
69. Respiratory Agents - Respiratory Antimuscarinics
70. Respiratory Agents - Respiratory Beta-Agonists - Long-Acting Respiratory Beta-Agonist
71. Respiratory Agents - Respiratory Beta-Agonists - Short-Acting Respiratory Beta-Agonist
72. Respiratory Agents - Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations
73. Toxicology Agents - Antidotes - Opiate Antagonists
74. Toxicology Agents - Substance Abuse Agents - Mixed Opiate Agonists/Antagonists

c. **For Possible Action**: Committee Discussion and Approval of the Drug Classes without Changes

7. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market and New Line Extensions

8. Closing Discussion

a. Public comments on any subject
b. Date and location of the next meeting
c. Adjournment

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to five minutes.

This notice and agenda have been posted at http://dhcfp.nv.gov/ and notice.nv.gov/.

Notice of this meeting and draft copies of the changes will be available on or after the date of this notice at the DHCFP Web site http://dhcfp.nv.gov/ Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a draft copy of the changes will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Colleen McLachlan at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701.

All persons that have requested in writing to receive the Public Hearings agenda have been duly notified by mail or e-mail.

We are pleased to make accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at: cmclach@dhcfp.nv.gov, in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Colleen McLachlan at (775) 684-3722.

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® * SAVELLA® * (Fibromyalgia only)	* PA required *No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® GRALISE® LIDODERM® * HORIZANT®
Tramadol and Related Drugs		
TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
Opiate Agonists		
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) FENTANYL PATCH BUTRANS®	**PA required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf Quantity limits apply to all Opioids	AVINZA® DOLOPHINE® DURAGESIC® PATCHES EXALGO® KADIAN® METHADONE METHADOSE® MS CONTIN® NUCYNTA® ER OPANA ER® OXYCODONE SR OXYMORPHONE SR XARTEMIS XR® ZOHYDRO ER®
Opiate Agonists - Abuse Deterrent		
EMBEDA® HYSINGLA ER®	Quantity limits apply to all Opioids	OXYCONTIN® XTAMPZA ER®

Preferred Products	PA Criteria	Non-Preferred Products
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
DICLOFENAC POTASSIUM DICLOFENAC TAB DR FLURBIPROFEN TAB IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB		CAMBIA ® POWDER CELECOXIB CAP DICLOFENAC SODIUM TAB ER DICLOFENAC W/ MISOPROSTOL TAB DUEXIS TAB ETODOLAC CAP ETODOLAC TAB ETODOLAC ER TAB INDOMETHACIN CAP ER KETOPROFEN CAP MEFENAM CAP MELOXICAM SUSP NAPRELAN TAB CR NAPROXEN TAB CR OXAPROZIN TAB TIVORBEX CAP VIMOVO TAB ZIPSOR CAP ZORVOLEX CAP
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE D OTC CETIRIZINE OTC LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non-preferred drug will be authorized.	ALLEGRA® CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP		BIAXIN® DIFICID®

Preferred Products	PA Criteria	Non-Preferred Products
ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
AVELOX® AVELOX ABC PACK® LEVOFLOXACIN		LEVAQUIN®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
AUVI-Q® * EPINEPHRINE® EPIPEN® EPIPEN JR.®	* PA required	ADRENACLICK® QL
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
CIMZIA® COSENTYX® ENBREL® HUMIRA® KINERET® ORENCIA® OTEZLA® SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ACTEMRA® ENTYVIO® ILARIS® INFLECTRA® REMICADE® STELARA® TALTZ®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® LEMTRADA® PLEGRIDY® ZINBRYTA®
Oral		
AUBAGIO®		

Preferred Products	PA Criteria	Non-Preferred Products
GILENYA® TECFIDERA®		
Specific Symptomatic Treatment		
AMPYRA® QL	PA required	
Cardiovascular Agents		
Antihypertensive Agents		
Angiotensin II Receptor Antagonists		
DIOVAN® DIOVAN HCTZ® LOSARTAN LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN® VALSARTAN
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)		
BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Regular Release)	*Restricted to ICD-10 codes J40-J48	SOTYLIZE®

Preferred Products	PA Criteria	Non-Preferred Products
NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Direct Renin Inhibitors		
TEKAMLO® TEKTURNA® TEKTURNA HCT® VALTURNA®		AMTURNIDE®
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
LETAIRIS® ORENITRAM® SILDENAFIL TRACLEER®		ADCIRCA® ADEMPAS® OPSUMIT® REVATIO ® UPTRAVI® NEW

Preferred Products	PA Criteria	Non-Preferred Products
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
ZETIA®		
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR®
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM

Preferred Products	PA Criteria	Non-Preferred Products
		SORILUX® TACLONEX® VECTICAL®
Topical Analgesics		
LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS VOLTAREN® GEL		EMLA® FLECTOR® LIDODERM® QL LIDAMANTLE® PENNSAID®
Topical Anti-infectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL®	PA required if over 21 years old	 ACZONE GEL® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)		
CICLOPIROX SOLN TERBINAFINE TABS	PA required	JUBLIA® KERYDIN® PENLAC® ITRACONAZOLE
Topical Antivirals		
ABREVA® DENAVIR® ZOVIRAX®, OINTMENT		
Topical Scabicides		
 NIX® PERMETHRIN RID®	* PA required	EURAX® LINDANE MALATHION NATROBA® *

Preferred Products	PA Criteria	Non-Preferred Products
SKLICE®		OVIDE® ULESFIA®
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE ELIPHOS® RENAGEL® RENVELA®		AURYXIA ® FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
DICLEGIS® OTC DOXYLAMINE 25mg / PYRIDOXINE 10mg EMEND®		
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	

Preferred Products	PA Criteria	Non-Preferred Products
Proton Pump Inhibitors (PPIs)		
NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®
Functional Gastrointestinal Disorder Drugs (New)		
AMITIZA® * LINZESS®	* PA required for Opioid Induced Constipation	MOVANTIK® * RELISTOR® *
Gastrointestinal Anti-inflammatory Agents		
ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		APRISO® ASACOL HD® COLAZAL® GIAZO® LIALDA ®
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
AVODART® FINASTERIDE		DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN CARDURA® FLOMAX® MINIPRESS® PRAZOSIN

Preferred Products	PA Criteria	Non-Preferred Products
		RAPAFLO® UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL SAVAYSA®* WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	
Injectable		
ARIXTRA® ENOXAPARIN FRAGMIN®		FONDAPARINUX INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL PROCRIT® QL	PA required Quantity Limit	EPOGEN® QL OMONTYS® QL
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL®	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® ZONTIVITY®

Preferred Products	PA Criteria	Non-Preferred Products
CLOPIDOGREL DIPYRIDAMOLE		
Hormones and Hormone Modifiers		
Androgens		
ANDROGEL® ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE (Precose®) GLYSET® PRECOSE® SYMLIN® (PA required)		CYCLOSET®
Biguanides		
FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics		
BYDUREON® * BYETTA® * TANZEUM® TRULICITY® VICTOZA® *	* PA required	
Insulins (Vials, Pens and Inhaled)		
APIDRA®		AFREZZA®

Preferred Products	PA Criteria	Non-Preferred Products
HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		BASAGLAR® NEW HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® JARDIANCE®		GLYXAMBI® INVOKAMET® INVOKAMET® XR SYNJARDY® XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS®		

Preferred Products	PA Criteria	Non-Preferred Products
ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®
Nasal Calcitonins		
MIACALCIN®		FORTICAL® CALCITONIN-SALMON
Restless Leg Syndrome Agents		
PRAMIPEXOLE REQUIP XL		HORIZANT® MIRAPEX®

	Preferred Products	PA Criteria	Non-Preferred Products
	ROPINIROLE		MIRAPEX® ER REQUIP
Skeletal Muscle Relaxants			
	BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents			
Alzheimers Agents			
	DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE NAMENDA® XR TABS RIVASTIGMINE CAPS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER NAMENDA® TABS NAMZARIC® RAZADYNE® RAZADYNE® ER
Anticonvulsants			
	BANZEL® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPITOL® ETHOSUXIMIDE FELBATOL® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR® LAMACTAL ODT® LAMACTAL XR® LAMICTAL®	PA required for members under 18 years old	APTIOM® BRIVIACT® FYCOMPA® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®

Preferred Products	PA Criteria	Non-Preferred Products
LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE (IR AND ER) TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines		
CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM DIAZEPAM rectal soln KLONOPIN® TRANXENE T-TAB® VALIUM®	PA required for members under 18 years old	ONFI®
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK®	PA required for members under 18 years old	

Preferred Products	PA Criteria	Non-Preferred Products
PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Serotonin-Receptor Agonists		
RELPAX® RIZATRIPTAN ODT SUMATRIPTAN NASAL SPRAY SUMATRIPTAN INJECTION SUMATRIPTAN TABLET	PA required for exceeding Quantity Limit	AMERGE® AXERT® FROVA® IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN SUMAVEL® TREXIMET® ZECUITY® TRANSDERMAL ZOMIG® ZOMIG® ZMT
Antiparkinsonian Agents		
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
Carbonic Anhydrase Inhibitors/Beta-Blockers		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LEVOBUNOLOL METIPRANOLOL SIMBRINZA® TIMOLOL DROPS/ GEL SOLN		ALPHAGAN® BETAGAN® BETOPTIC ® COSOPT® COSOPT PF® OCUPRESS® OPTIPRANOLOL® TIMOPTIC® TIMOPTIC XE® TRUSOPT®
Ophthalmic Prostaglandins		
LATANOPROST LUMIGAN® TRAVATAN®		TRAVOPROST XALATAN® ZIOPTAN®

Preferred Products	PA Criteria	Non-Preferred Products
TRAVATAN Z®		
Ophthalmic Antihistamines		
ALAWAY® BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRA/DEXAME SUS % ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO®		ACULAR® ACULAR LS® ACUVAIL®

Preferred Products	PA Criteria	Non-Preferred Products
KETOROLAC NEVANAC®		BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
RESTASIS® NEW		XIIDRA® NEW
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® ADZENYS® AMPHETAMINE SALT COMBO IR DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® INTUNIV® METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® AMPHETAMINE SALT COMBO XR APTENSIO XR® CONCERTA® DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® KAPVAY® METADATE ER® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR	PA required for members under 18 years old	APLENZIN® BRINTELLIX®

Preferred Products	PA Criteria	Non-Preferred Products
BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	* PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* Preferred for ICD-10 code G31.83 OLANZAPINE QUETIAPINE REXULTI® RISPERIDONE SAPHRIS® SEROQUEL XR® ZIPRASIDONE	**PA required for Ages under 18 years old** **PA Forms:** https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE QUETIAPINE XR NEW RISPERDAL® SEROQUEL® VRAYLAR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM®	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA®

Preferred Products	PA Criteria	Non-Preferred Products
TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM ZOLPIMIST®		DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
ASTEPRO® DYMISTA® PATANASE®		AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
Respiratory Corticosteroids		
ARNUITY ELLIPTA® ASMANEX® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	ALVESCO® AEROSPAN HFA® BUDESONIDE NEBS*
Nasal Corticosteroids		
FLUTICASONE NASONEX®		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST®

Preferred Products	PA Criteria	Non-Preferred Products
		ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Respiratory Antimuscarinics		
ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA ® SEEBRI NEOHALER® SPIRIVA RESPIMAT® TUDORZA®
Respiratory Beta-Agonists		
Long-Acting Respiratory Beta-Agonist		
FORADIL® SEREVENT DISKUS® QL STRIVERDI RESPIMAT®		ARCAPTA NEOHALER® BROVANA® PERFOROMIST NEBULIZER®
Short-Acting Respiratory Beta-Agonist		
ALBUTEROL NEB/SOLN LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL	* PA required	LEVALBUTEROL* HFA NEW PROAIR® HFA PROAIR RESPICLICK® VENTOLIN HFA® XOPENEX® Solution* QL
Respiratory Corticosteriod/Long-Acting Beta-Agonist Combinations		
ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Respiratory Long-Acting Antimuscarinic/Long-Acting Beta-Agonist Combinations		
ANORO ELLIPTA® STIOLTO RESPIMAT®		UTIBRON NEOHALER ®
Toxicology Agents		
Antidotes		
Opiate Antagonists		
NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
Mixed Opiate Agonists/Antagonists		
BUNAVAIL® SUBOXONE® ZUBSOLV®	PA required for class	BUPRENORPHINE/NALOXONE

2. Standard Preferred Drug List Exception Criteria
Drugs that have a “non-preferred” status are a covered benefit for recipients if they meet the coverage criteria.
a. Coverage and Limitations
1. Allergy to all preferred medications within the same class;
2. Contraindication to or drug-to-drug interaction with all preferred medications within the same class;
3. History of unacceptable/toxic side effects to all preferred medications within the same class;
4. Therapeutic failure of two preferred medications within the same class.
5. If there are not two preferred medications within the same class therapeutic failure only needs to occur on the one preferred medication;
6. An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or a FDA-approved indication;
7. Antidepressant Medication – Continuity of Care.
Recipients discharged from acute mental health facilities on a nonpreferred antidepressant will be allowed to continue on that drug for up to 90 days following discharge. After 90 days, the recipient must meet one of the above five (5) PDL Exception Criteria; or
8. For atypical or typical antipsychotic, anticonvulsant and antidiabetic medications the recipient demonstrated therapeutic failure on one preferred agent.
b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms/aspx.

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective through June 30, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

(d) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty; and

(d) The criteria for prescribing an atypical or typical antipsychotic medication, anticonvulsant medication or antidiabetic medication that is not on the list of preferred drugs to a patient who experiences a therapeutic failure while taking a prescription drug that is on the list of preferred prescription drugs.

4. Except as otherwise provided in this subsection, the list of preferred prescription drugs established pursuant to subsection 1 must include, without limitation, every therapeutic prescription drug that is classified as an anticonvulsant medication or antidiabetic medication that was covered by the Medicaid program on June 30, 2010. If a therapeutic prescription drug that is included on the list of preferred prescription drugs pursuant to this subsection is prescribed for a clinical indication other than the indication for which it was approved as of June 30, 2010, the Committee shall review the new clinical indication for that drug pursuant to the provisions of subsection 5.

5. The regulations adopted pursuant to this section must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

6. The Medicaid program must make available without prior authorization atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness, anticonvulsant medications and antidiabetic medications for a patient who is receiving services pursuant to Medicaid if the patient:

(a) Was prescribed the prescription drug on or before June 30, 2010, and takes the prescription drug continuously, as prescribed, on and after that date;

(b) Maintains continuous eligibility for Medicaid; and

(c) Complies with all other requirements of this section and any regulations adopted pursuant thereto.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985)

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective July 1, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness of a patient who is receiving services pursuant to Medicaid;

(b) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

(g) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

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(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty.

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(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985, effective July 1, 2015)

Definition of "Therapeutic Alternative"

A "Therapeutic Alternative" is defined by the AMA as: "Drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses."

BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Acting Administrator

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Nevada Medicaid

PHARMACY AND THERAPEUTICS COMMITTEE

DRAFT MEETING MINUTES

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee held a public meeting on March 23, 2017 beginning at **1:00 p.m.** at the following location:

North Nevada Location:
Silver State Health Insurance Exchange
2310 S. Carson St
Ste. 3A
Carson City, NV 89701

South Nevada Location:
Silver State Health Insurance Exchange
150 N. Stephanie St
Ste. 100
Henderson, NV 89074

Committee Members Present:
Mark Decerbo, Pharm.D.; Shamim Nagy, MD; Mike Hautekeet, Pharm.D.; Joseph Adashek, MD; Nikki Beck, Pharm.D.; Christopher Highley, MD; Weldon Havins, MD; Adam Zold, Pharm.D.

Committee Members Absent:
Evelyn Chu, Pharm.D.

Others Present:
DHCFP:
Mary Griffith, RN, Pharmacy Services Specialist; Gabriel Lither, Deputy Attorney General; Sherri Eggleston

HPES:
Beth Slamowitz, Pharm.D.

Optum:
Carl Jeffery, Pharm.D., Kevin Whittington, RPh; Daniel Medina

Others:
John Sandstrom, Shire; Rob Bigham, Shire; Nana Numapau, Boehringer Ingelheim; Jennifer Lauper, BMS; Samantha Sweeney, Otsuka; Sane Guo, Otsuka; Melissa Walsh, Novartis; Tom O,Connor, Novartis; Mark Schwartz, GSK; Leon Ravin, DPBH; Joe Schreck, Allergan; Chris Stanfield, Supernus; Addie Meyers, Merck; Coleen Lawrence, Moxy; Phil Walsh, Sunovian; Cynthia Albert, Merck; Dave West, United Therapeutics; Aimee Dorman, United Therapeutics; Mike Strong, Novo Nordisk; Toby Damron, Novo Nordisk

AGENDA

1. Call to Order and Roll Call

The meeting is called to order at 12:58 PM.

Roll Call

North:

Christopher Highley: Here
Michael Hautekeet: Here
Beth Slamowitz: Beth Slamowitz, HPE
Sherri Eggleston: Sherri Eggleston, DHCFP

South:

Weldon Havins: Present
Joseph Adashek: Present
Adam Zold: Present
Shamim Nagy, Chair: Present
Mark Decerbo: Present
Mary Griffith: Mary Griffith, DHCFP
Carl Jeffery: Carl Jeffery, OptumRx
Kevin Whittington: Kevin Whittington, OptumRx
Gabe Lither: Gabe Lither, Senior Deputy Attorney General

2. Public Comment

Shamim Nagy, Chair: Any public comments?

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from December 8, 2016.

Shamim Nagy, Chair: We need a motion to approve the minutes from the last meeting.

Weldon Havins: So moved.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

b. Status Update by DHCFP

Shamim Nagy, Chair: Status update from the DHCFP.

Mary Griffith: This is Mary Griffith, the pharmacy specialist for the DHCFP. I want to welcome everyone to our March Pharmacy and Therapeutics Committee meeting. This is our first split meeting. We wanted our members in the north to be able to continue their normal business as much as possible. This is a learning curve for us.

Regarding status updates, we have some personnel changes. Duane Young is the new chief for pharmacy. He comes to us from the Division of Public and Behavior Health. He has a lot of knowledge of the ACA. Shannon Sprout was the Chief and is now the Deputy Administrator, replacing Betsy Aiello who retired last month.

Medicaid Services Manual Chapter 1200 changes are scheduled to go to April 26 public hearing. Included in those changes is the requirement for opioids be a seven day dispense only on initial prescriptions. The policy on dispensing practitioners will be included and be effective April 27, 2017.

The DHCFP has been working with the Legislature.

For housekeeping, for the P&T Committee, Carl Jeffery will display the proposed preferred drug list, if your drug is recommended as preferred, you do not need to testify. Because we have a split committee, the voting will be called out by name so we can record the votes. If there are questions, I encourage you to not all talk at once or make sure we acknowledge that you have a question. That is the end of my update.

Shamim Nagy, Chair: Do we have any public comments?

4. Established Drug Classes

a. Psychotropic Agents: Atypical Antipsychotics – Oral

Shamim Nagy, Chair: We will start with established drug classes, psychotropic agents, atypical antipsychotic, oral agents. Do we have any public comment? None.

Carl, could you give us your update?

Carl Jeffery: I hope this will be a quick review. We are bringing this up because there is a new generic for Seroquel XR. Right now, since there is only one manufacturer of the generic, we are recommending it be non-preferred. I am showing the indications on the screen, the generic has the same indications as the brand. I think it will be available from multiple manufacturers pretty soon. Optum recommends the Committee consider the drugs in this class to be clinically and therapeutically equivalent.

Weldon Havins: I move they be considered clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the quetiapine XR, the generic for the Seroquel XR be considered non-preferred.

Mark Decerbo: I move to approve as presented on the screen.

Adam Zold: Second.

Christopher Highley: I have a question, are there any other approved antipsychotic extended release that are generic at this time?

Carl Jeffery: There are some that are just once a day, not necessarily extended release, like aripiprazole.

Christopher Highley: Ok, that works for me, I agree with the motion.

Weldon Havins: I have a question too. I noticed some material with the NRS422, it says the Medicaid program must make available without prior authorization atypical and typical antipsychotic medications. Are you making this non-preferred?

Mary Griffith: NRS422.4025 allows for oral typical and atypical antipsychotics to be on the PDL as long as they were not on the market before 2010.

Gabe Lither: All of the products on the market at that time were grandfathered in. Since then, we can make new rules going forward.

Weldon Havins: Ok, thank you. I appreciate the clarification.

Voting: Ayes across the board, the motion carries.

b. Respiratory Agents: Short-Acting Respiratory Beta-Agonists

Shamim Nagy, Chair: Respiratory agents, short-acting respiratory beta-agonists. Do we have any public comment? None.

Carl Jeffery: This is another easy one, we have a newly available generic for the Xopenex HFA, levalbuterol HFA. This is straight forward AB rated generic, it really isn't any different than the brand that is available. Optum recommends the Committee consider these to be clinically and therapeutically equivalent.

Weldon Havins: I move that these be considered clinically and therapeutically equivalent.

Joseph Adashek: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends the new generic levalbuterol HFA be considered non-preferred and the rest of the class remain the same.

Joseph Adashek: Will brand name Xopenex remain preferred?

Carl Jeffery: Yes, the brand Xopenex HFA will remain preferred.

Joseph Adashek: I move we accept the recommendations.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

5. Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. Cardiovascular Agents: Antihypertensive Agents: Vasodilators – Oral

Shamim Nagy, Chair: Established drug classes being reviewed due to the release of new drugs. Cardiovascular agents, antihypertensive agents, vasodilators, oral. Do we have any public comment? None.

Carl Jeffery: Uptravi is a relatively new product, it has been available for about a year. We barely missed it the last time we reviewed the class. We are talking about the oral agents today, there are also inhaled and injectable products in this class. I broke out the drugs to see the classes. There are three classes, and you can see the indications. The PDE 5 and sGC Stimulators all work on the prostaglandin pathway. The endothelin receptors, PCA and PRA are all listed. When we talk about pulmonary hypertension, there are three basic pathways that we consider, prostacyclins, endothelins and nitric oxide pathways. I may have misspoke on the previous slide the prostacyclin pathway is the PCA's and the prostacyclin receptor agonist. The active drugs that do affect the prostacyclin is Uptravi and Orenitram. The others are available inhaled, IV or sub q. Speaking of Uptravi specifically, the GRIPHON study had about 1100 patients. It compared to placebo and it had a significant reduction in endpoints of all-cause death and complications. It didn't show any mortality reduction, but it did show a benefit of either reducing hospitalizations or disease progression. There were several meta-analysis studies done. The first here is 18 trials, about 4000 patients. Looking at the therapeutic benefit was done before Uptravi was available, but you can see PDE-5 inhibitors show a significant benefit. The next one was 14 trials with about 2200 patients looking at overall survival. Really only the patients getting the IV formulation showed a benefit, the oral and sub q did not show a significant benefit. Another study with 21 trials and about 5000 patients showed all classes reduce clinical worsening. There were lots of other smaller studies, IV was better, combo is better than monotherapy. One analysis showed prostacyclin was better than some of the other agents. The treatment guidelines have not been updated since the release of Uptravi. But they

do start with monotherapy and then move to parenteral therapy with the more severe disease. The European society has been updated since Uptravi and they recommend any oral agent, no preference for one over another. With this information, Optum recommends the class be considered clinically and therapeutically equivalent.

Joseph Adashek: I move we accept the recommendation that they are therapeutic alternatives.

Weldon Havins: Second.

Voting: Ayes, across the board, the motion carries.

Carl Jeffery: Because Orenitram is a similar agent and uses the same pathway as Uptravi and is preferred, Optum recommends Uptravi be non-preferred.

Adam Zold: I move to accept Optum's recommendation.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

b. Hormones and Hormone Modifiers: Antidiabetic Agents – Insulins (Vials, Pens and Inhaled)

Shamim Nagy, Chair: The next item is hormones and hormone modifiers, antidiabetic agents, insulin. Do we have any public comment? None.

Carl Jeffery: We have another kind of generic, Basaglar is the same molecular entity as Lantus. They used an abbreviated approval process to get it approved through the FDA. This is called a follow-on biologic. This has been available since late last year. Safety and efficacy are similar to Lantus. They did a comparison with Lantus in a non-inferiority study. Really nothing else showing it is superior to Lantus. Optum recommends this class be considered clinically and therapeutically equivalent.

Joseph Adashek: I move we accept the recommendations from Optum.

Weldon Havins: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends Basaglar be non-preferred since the Lantus is preferred and they are similar agents.

Michael Hautekeet: I make a motion to accept Optum's recommendation.

Mark Decerbo: Second.

Voting: Ayes across the board, the motion carries.

c. Hormones and Hormone Modifiers: Antidiabetic Agents – Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

Carl Jeffery: Dr. Nagy, the SGLT2's the product we had hoped to review at this time is not yet available on the market. We usually wait until the product is on the market until we review it. We request to bypass this review.

6. Proposed New Drug Classes

a. Ophthalmic Agents: Opthalmics for Dry Eye Disease

Shamim Nagy, Chair: Proposed new class, new subclass, ophthalmic agents, ophthalmics for dry eyes.

John Sandstrom: My name is John Sandstrom from Shire Medical Affairs. I want to thank Optum for the thorough review. Xiidra is the first and only FDA approved medication for the treatment of signs and symptoms of dry eye disease. Dry eye disease is a multifactorial disease causing discomfort of the tears and ocular surface that results in symptoms of discomfort, visual disturbance with potential damage to the ocular surfaces. Dry eyes is one of the most common complaints to eye care professionals and is often chronic.

Some highlights, studies, efficacy and safety of Xiidra was presented.

I will leave it open to any questions.

Carl Jeffery: We do have some comments from the web.

Rick Croshella: My name is Rick Croshella, I am an MSL for Allergan. I just wanted to mention a couple things about Restasis. It is approved for dry eyes. It increases tear production in patients related to ocular inflammation associated with KCS. Restasis is believed to be a partial immune modulator and has been well studied for over 13 years. It has been proven to be safe and well tolerated with limited side effects. It has no detectable levels in the blood.

Some studies and the mechanism of action was presented.

Only Restasis has been shown to be more effective than artificial tears. I will take any questions.

Carl Jeffery: I don't see any other public comment. This is a new class we are proposing. There are two drugs in this class. Before we only had Restasis, Xiidra is relatively new. They have similar indications with dry eye disease. I am looking for Dr. Havins to provide some input too. The dry eye disease is a common complaint. Restasis is cyclosporine, it really isn't known how it works but is thought to help with inflammation. With two randomized placebo controlled trials, about 870 patients and open label extension, the treatment group improved over baseline. It works about the same as punctal plugs for efficacy, but the punctal plugs work much faster. With the review of about 18 randomized trials, 100% of the studies improve dry eyes over placebo. Xiidra is a small molecule, not something that is not currently available. It is T-cell mediated inflammation response modifier. The exact mechanism is unknown but probably related to decreasing inflammation. Four 12 week studies with almost 1200 patients. Dry eye scores reduced over placebo, visual related scores are improved, and corneal staining reduced. Guidelines have not been updated to incorporate Xiidra yet, but they do include cyclosporine for

the treatment of severe dry eyes. Optum recommends this class be considered clinically and therapeutically equivalent.

Mark Decerbo: Somewhat off topic, but thank you to you and Optum. We have had a cornucopia of classes before and I don't think this was a class before, but I think it is a new class, but thank you for picking some of these out into more pharmacological categories.

Carl Jeffery: Thanks, and just for clarification, this is a new class.

Weldon Havins: I think the most important statement here is there are no comparative trials of cyclosporine to this new class with Xiidra. Restasis has been around a long time. In my experience Restasis is helpful in those who have an inflammatory component to their dry eyes. In my experience it does not have any superiority over artificial tears or punctal plugs in those that do not have an inflammatory component. It would be interesting to see a head-to-head study with these two drugs. I move that these are clinically and therapeutically equivalent. It is with some degree a movement of ignorance because I don't know that to be an absolute fact, but based on the information that we have.

Adam Zold: Second.

Voting: Ayes across the board, the motion carries.

Carl Jeffery: Optum recommends making Restasis preferred and Xiidra non-preferred.

Weldon Havins: I move we accept the recommendations from Optum that Restasis is preferred and Xiidra is non-preferred.

Michael Hautekeet: Second.

Voting: Ayes across the board, the motion carries.

7. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions

Shamim Nagy, Chair: Report on new drugs to the market by Optum.

Carl Jeffery: We have been talking about these for a few quarters now. A new generic for Pristiq, Emend and Zetia. They will have spots on our PDL and will have an impact. Some new drugs that I think will be more of a discussion are Qtern, a combination of dapagliflozin and saxagliptin. Then Soliqua and Xultophy are combinations of insulins and GLP-1. I think for the discussion on which classes they go into, we have to look at the classes that are similar and should be tried first. It makes sense to put these in the insulin class because someone would be on insulin before getting one of these. Trulance is a new treatment for idiopathic constipation. It was a new class we added at the last meeting. A couple new extended release opioid products, Vantrela ER and Arymo and a few others that are coming out too. These will probably be on our June agenda and there is another one too. A couple new formulations with Vyvance with a new chewable tablet. Synjardy will be coming back again with the label update and the cardiovascular risk reduction studies.

Weldon Havins: If someone has type 2 diabetes and starts on metformin and then moves to add a GLP-1. Is that ok or is there something that needs to be tried before that?

Carl Jeffery: No, they could move to a GLP-1, there are not any restrictions as long as they request a preferred GLP-1. I think they have to have a diagnosis of diabetes now.

Shamim Nagy, Chair: You go with a clinical algorithm?

Carl Jeffery: We don't really go with an algorithm with the P&T, it is just the preferred drug list. We don't have step therapy per se. The DUR Board could add some criteria to have to try some therapies before moving to another.

Mark Decerbo: In general, we as a Committee, we are not following an algorithm, but the algorithms are based on clinical data and then the two comport with one another like the two GLP-1s like Victoza. It has got the cardiovascular data now and it is on the preferred drug list. And I think you raised a good point, what do we do with combo products moving forward? Hopefully, these are hand-in-hand and we don't need too much from the DUR Board. We are following evidence in what is out there with results and treatment guidelines.

Weldon Havins: For the biosimilars, where do those stand?

Carl Jeffery: We have one biosimilar we reviewed last time with the immunomodulators. There are more coming out and we will review them as individual products going forward.

Weldon Havins: Are we only going to review those the FDA has approved?

Carl Jeffery: Right, approved and on the market. We need some market data before we can do a review on those.

8. Closing Discussion

Shamim Nagy, Chair: Moving to closing discussion. Do we have any public comment? No public comment. Date and location of the next meeting.

Carl Jeffery: I have June 22 at 1:00. We have booked this room for the remainder of the year.

Shamim Nagy, Chair: The meeting is adjourned.

Meeting adjourned at 1:45 PM.

Therapeutic Class Overview
Opioids, Long Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology. Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing reinjury. In contrast, chronic pain, often defined as pain persisting for over three to six months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2012*).
  - Chronic pain is estimated to affect 100 million Americans and the total annual incremental cost of health care in 2010 due to pain ranges from $560 billion to $635 billion in the United States (U.S.). This includes medical costs and costs related to disability days and lost wages and productivity (*American Academy of Pain Medicine [AAPM] 2014*).
- Pain may be classified as nociceptive pain and neuropathic pain.
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics (*Cohen et al 2012*).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2012*).
  - Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics, alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained release formulations (*Cohen et al 2012*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2012, The Medical Letter 2013*).
- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explains the FDA's current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also makes recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance does not address generic opioids. Subsequently in March 2016, the FDA issued draft guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2016*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product's abuse deterrent properties consistent with the FDA's guidance for industry (*Hale et al 2016*).
  - Since the approval of reformulated OxyContin, several other long-acting opioids have been approved with abuse deterrent labeling, including, Arymo ER (morphine), Embeda (morphine and naltrexone), Hysingla ER (hydrocodone), Morphabond (morphine), Targiniq ER (oxycodone and naloxone), Troxyca ER (oxycodone and naltrexone), Vantrela ER (hydrocodone), and Xtampza ER (oxycodone); however, Targiniq ER, Troxyca ER, and Vantrela ER have yet to launch (*Drugs@FDA 2017, Hale et al 2016*).

- A number of federal agencies have recently implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The Drug Enforcement Agency (DEA) issued a nationwide alert regarding fentanyl products laced with heroin, causing significant drug incidents and overdoses nationwide. The U.S. Office of Disease Prevention and Health Promotion announced a new interactive training tool, "Pathways to Safer Opioid Use," which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment (*CMS 2017, DEA 2016, Office of Disease Prevention and Health Promotion 2015, NIDA 2015*)
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12) (*Prescribing information: Dolophine 2017, methadone oral solution 2016, METHADOSE 2016*).
- Included in this review are the long-acting opioids which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2017*). TARGINIQ ER, TROXYCA ER, and VANTRELA ER are not included in this review as they have not been launched yet.
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2017*).
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Arymo ER, Avinza¶, Kadian, Morphabond MS Contin (morphine sulfate)	✔
Butrans (buprenorphine)	✔
Dolophine, Methadose (methadone)	✔
Duragesic (fentanyl)	✔
Exalgo (hydromorphone)	✔
Hysingla ER† Zohydro ER§ (hydrocodone bitartrate)	-
Levorphanol	✔
Nucynta ER (tapentadol)	-
Opana ER* (oxymorphone)	✔
OxyContin†, Xtampza ER (oxycodone)	✔

Drug	Generic Availability
Combination Products	
Embeda† (morphine sulfate/ naltrexone)	-
Xartemis XR (oxycodone hydrochloride/ acetaminophen)	-

*Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.

†Approved as an abuse deterrent (AD) formulation which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*

‡OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.

§In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid.

¶Avinza branded products were discontinued by Pfizer in July 2015.

(*Drugs@FDA 2017, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
Pain Management												
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔	✔		✔ *	✔	✔	✔	✔	✔	
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †				
Management of moderate to severe pain in patients where an opioid analgesic is appropriate.					✔							
Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		✔ ‡		✔ ‡								
For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.												✔
Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate										✔		
Opioid Addiction												
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔						
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔						
Limitations of Use												
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products	
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone	oxycodone/ acetaminophen
use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.												
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔		✔	✔		✔	✔	✔	✔	✔	✔	

*Methadone tablets only
†OxyContin only
‡Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

(Prescribing information: Arymo ER 2017, Butrans 2016, Dolophine 2017, Duragesic 2016, Embeda 2016, Exalgo 2016, Hysingla ER 2016, Kadian 2016, levorphanol 2015, methadone oral solution 2016, Methadose 2016, Morphabond 2017, MS Contin 2016, Nucynta ER 2016, Opana ER 2016, OxyContin 2016, Xartemis XR 2014, Xtampza ER 2016, Zohydro ER 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al [a], 2010, Gordon et al [b], 2010, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Ma et al 2008, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2013, Wild et al 2010*).

- Recent systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N=39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blinded studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only double-blinded, randomized controlled trials for efficacy assessments; open-label and controlled observational studies were allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and “current pain in the morning;” however, the “worst pain in the past 24 hours” and “current pain in the evening” were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- Arymo ER and Morphabond were approved based on bioequivalence to MS Contin. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturers relied on previous findings of efficacy and safety for MS Contin (*FDA Summary Review: Arymo ER 2017, Morphabond 2017*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Dubinsky et al 2004, Chou et al 2009, Hochberg et al 2012, Paice et al 2016*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).

- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (*Dowell et al 2016*):
  - Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (category A, evidence 3).
  - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
  - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
  - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of ER/long-acting opioids (category A, evidence 4).
  - Clinicians should prescribe opioids at the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day (category A, evidence 3).
  - Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (category A, evidence 4).
  - Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
  - Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
  - Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
  - When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).

- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:
- Category A: Applies to all persons; most patients should receive the recommended course of action.
- Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:
- Type 1: Randomized clinical trials or overwhelming evidence from observational studies.
- Type 2: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
- Type 3: Observational studies or randomized clinical trials with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.

- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
  - Strong).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for all ER and long-acting opioids included in this review, with the exception of levorphanol. This program has been updated to include new formulations and medications. The REMS program is part of the national prescription drug abuse plan announced in 2011 to combat prescription drug misuse and abuse. Program components include prescriber education and training, patient education, and a communication plan for prescribers (*FDA REMS 2017*).

- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance.
- Most long-acting opioids are associated with boxed warnings regarding the potential for abuse and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, an interaction with alcohol, and accidental ingestion risks. Dolophine and methadone products have additional boxed warnings regarding life-threatening QT prolongation. Duragesic, Hysingla ER, OxyContin, and Zohydro ER also have a Boxed Warning for an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers). An additional Boxed Warning for Duragesic cautions against exposure to heat due to increases in fentanyl release.
- Key contraindications across the class include acute or severe bronchial asthma, significant respiratory depression, and known or suspected paralytic ileus.
- There are multiple warnings and precautions with each agent. Key safety concerns associated with the opioid analgesics include respiratory depression, driving and operating machinery, hypotension, interactions with other central nervous system (CNS) depressants, neonatal opioid withdrawal syndrome, use in special populations, and use in those with gastrointestinal conditions.
- The frequency of adverse reactions varies to some degree with each agent; however, overall adverse reactions are similar within the class. The most common adverse events in adults include nausea, vomiting, constipation, and somnolence.
- OxyContin has recently been approved in patients aged ≥11 years. The most frequent adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.
- In March 2016, the FDA issued a drug safety communication warning about several safety issues with opioids and describing new class-wide labeling requirements. The warnings include the following (*FDA Drug Safety Communication 2016*):
  - Opioids can interact with antidepressants and migraine medications to cause serotonin syndrome.
  - Taking opioids may rarely lead to adrenal insufficiency.
  - Long-term opioid use may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- In August 2016, the FDA announced that it is requiring class-wide changes to drug labeling, including patient information, in order to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines (*FDA Drug Safety Communication 2016*).
  - Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concomitantly. Risks include extreme sleepiness, respiratory depression, coma, and death.
- On March 14, 2017, the FDA Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to 8, that the benefits of reformulated Opana ER (which did not originally gain the labeling describing potential abuse deterrent properties) no longer outweigh its risks. This vote followed an FDA analysis of epidemiological data that indicated that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated (*FDA Advisory Committee 2017*). Following the FDA's official withdrawal request, the manufacturer (Endo) announced the voluntary market withdrawal of reformulated Opana ER (*Endo Press Release 2017*).

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. Please see a detailed description within the prescribing information for each agent regarding when a patient is considered opioid-tolerant and which strengths are appropriate in these patients.
- See prescribing information for detailed conversion recommendations as there are no established conversions from other opioid agents. When converting to an agent, it is better to underestimate need and monitor for breakthrough pain.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arymo ER, Avinza†, Kadian*, Morphabond, MS Contin (morphine sulfate)	ER capsules and tablets	Oral	Arymo ER, MS Contin: Every 8 to 12 hours Avinza: Once daily Morphabond: Every 12 hours Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans (buprenorphine)	Transdermal system	Topical	Administration every 7 days	• Not evaluated in patients with severe hepatic impairment and should be administered with caution.
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every three to five days; however some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require systems be applied at 48 hours)	• Avoid use in patients with severe renal impairment. • Avoid use in patients with severe hepatic impairment.
Exalgo (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe impairment, reduce the HYSINGLA dose to 1/2 the usual initial dose and start ZOHYDRO at the lowest dose of 10 mg every 12 hours. • HYSINGLA: In moderate to severe impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment. • Not recommended in patients with severe hepatic impairment.
Opana ER (oxymorphone)‡	ER tablets	Oral		• Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.
Combination Products				
Embeda (morphine sulfate/ naltrexone)	ER capsules	Oral	Once daily	• Renal dose adjustment may be required in severe renal impairment. • Hepatic dose adjustment may be required in severe hepatic impairment.
Xartemis XR (oxycodone/ acetaminophen)	ER tablets	Oral	Every 12 hours	

*Available only as brand name Kadian
†All Avinza branded products have been removed from the market.
§Available only as brand name OxyContin.
‡Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.

CONCLUSION

- Opioids have been the mainstay of pain treatment for a number of years, and there is well documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several long-acting opioid agents available which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen et al 2012*).
  - Xartemis XR is the only long-acting agent in class indicated for severe acute pain.
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has recently been FDA-approved as an option in pediatric patients, aged ≥11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary: OxyContin 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal buprenorphine which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Embeda (morphine sulfate/naltrexone), Hysingla ER (hydrocodone bitartrate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).

- Almost all long-acting opioids are part of the REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, OxyContin, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
  - Several generic long-acting opioids exist, including hydromorphone; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain. No single opioid is recommended over the others (*Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014*). Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Dubinsky et al 2004, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has recently been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*).

REFERENCES

- Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared to oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010;30(8):489-505.
- Agarwal A, Polydefkis M, Block B, et al. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Medicine. 2007;8(7):554-62.
- Allan L, Hays H, Jensen NH, et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ. 2001;322:1-7.
- Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl vs sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. Spine. 2005;30(22):2484-90.
- American Academy of Pain Medicine (AAPM) facts and figures on pain. The American Academy of Pain Medicine. Available at: http://www.painmed.org/patientcenter/facts_on_pain.aspx#incidence. Accessed March 24, 2016.
- Arymo ER prescribing information. Egalet US Inc. Wayne, PA. January 2017.
- Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17)9):1113-e88.
- Bao YJ, Hou W, Kong XY, et al. Hydromorphone for cancer pain. Cochrane Database Syst Rev. 2016;10:CD011108.
- Bekkering GE, Soares-Weiser K, Reid K, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Curr Med Res Opin. 2011 Jul;27(7):1477-91.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17:76(20):1758-65.
- Bruera E, Palmer JL, Bosnak S, et al. Methadone vs morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol. 2004;22(1):185-92.
- Butrans prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother. 2010 Aug;11(11):1787-804.
- Caldwell JR, Rappaport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open label extension trial. J Pain Symptom Manage. 2002;23:278-91.
- Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. Palliat Med. 2011 Jul;25(5):402-9.
- Centers for Medicare & Medicaid Services (CMS). Improving Drug Utilization Review Controls in Part D. Updated March 15, 2017. Available at: http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxUtilization.html. Accessed March 22, 2017.
- Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15(4):321-337.
- Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. J Pain. 2009 Feb;10(2):113-30.
- Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Int Med. 2007 Oct 2;147(7):478-91.

- Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-86.
- Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Current Medical Research and Opinion. 2004;20(9):1419-28.
- Cohen SP, Srinivasa NR. Chapter 29. Pain. In: Goldman L, Schafer AI. eds. Goldman's Cecil Medicine, 24e. Philadelphia, PA: Elsevier, Inc.; 2012. Available by subscription at: www.clinicalkey.com. Originally accessed October 2, 2015.
- Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomized trial. Osteoarthritis Cartilage. 2011 Aug;19(8):930-8.
- Dolophine prescribing information. Roxane Laboratories, Inc. Columbus, OH. January 2017.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep 2016;65:1-49. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?s_cid=rr6501e1_w#B1_down. Accessed March 22, 2017.
- Drug Enforcement Administration (DEA). FENTANYL (Trade Names: Actiq, Fentora, Duragesic). December 2016. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/fentanyl.pdf. Accessed March 22, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. March 22, 2017.
- Dubinsky RM, Kabbani H, El-Chami, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004;63:959.
- Duragesic prescribing information. Janssen Pharmaceutical, Inc. Titusville, NJ. December 2016.
- Embeda prescribing information. King Pharmaceuticals, Inc. Bristol, TN. December 2016.
- Endo Pharmaceutics. Press Release. Endo Provides Update On OPANA ER. July 6, 2017. Available at: http://phx.corporate-ir.net/phoenix.zhtml?c=231492&p=irol-newsArticle_print&ID=2284981. Accessed July 21, 2017.
- Exalgo prescribing information. Mallinckrodt LLC. Hazelwood, MO. December 2016.
- Food and Drug Administration (FDA). FDA statement: Original Opana ER relisting determination. May 10, 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm351357.htm. Accessed March 22, 2017.
- FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed March 22, 2017.
- FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 21, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed March 21, 2017.
- FDA Industry Guidance. Guidance for Industry: Abuse-Deterrent Opioid – Evaluation and Labeling. April 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed March 22, 2017.
- FDA Industry Guidance. Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (draft guidance). March 2016. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf. Accessed March 22, 2017.
- FDA Risk Evaluation and Mitigation Strategy (REMS). Extended-release (ER) and long-acting (LA) opioid analgesics REMS. Updated February 2017. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf. Accessed March 24, 2017.
- FDA Briefing Document. Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting. March 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545760.pdf. Accessed March 24, 2017.
- FDA Summary Minutes. Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting. May 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM509895.pdf. Accessed March 22, 2017.
- FDA Summary Review. Application number: 022272Orig1s027 (OxyContin). August 13, 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022272Orig1s027SumR.pdf. Accessed March 22, 2017.
- FDA Summary Review. Application number: 022272Orig1s027 (Arymo ER). January 9, 2017. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208603Orig1s000SumR.pdf. Accessed March 22, 2017.
- Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. Br J Anaesth. 2011 Sep;107(3):319-28.
- Finkel JC, Finley A, Greco C, et al. Transdermal fentanyl in the management of children with chronic severe pain. Results from an international study. Cancer. 2005;104:2847-57.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.
- Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. Neurology. 2003;60:927-34.
- Gordon A, Rashiq S, Moulin DE, et al [a]. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. Pain Res Manag. 2010 May-Jun;15(3):169-78.
- Gordon A, Callaghan D, Spink D, et al [b]. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010 May;32(5):844-60.
- Hale ME, Moe D, Bond M, Gasior M, Malamut R. Abuse-deterrent formulations of prescription opioid analgesics in the management of chronic noncancer pain. Pain Manag. 2016;6(5):497-508.
- Hale M, Tudor IC, Khanna S, et al. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, non inferiority analysis. Clin Ther. 2007;29(5):874-88.
- Hale M, Khan A, Kutch M, et al. Once-daily OROS hydromorphone ER compared to placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010;26(6):1505-18.

- Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.
- Hysingla ER prescribing information. Purdue Pharmaceuticals, L.P. Stamford, CT. December 2016.
- Kadian prescribing information. Actavis Elizabeth LLC. Morristown, NJ. December 2016.
- Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) vs prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group non inferiority study. Clin Ther. 2009 Mar;31(3):503-13.
- Katz N, Hale M, Morris D, et al. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. Postgrad Med. 2010 Jul;122(4):112-28.
- Katz N, Kopecky EA, O'Connor M, Brown RH, Fleming Ab. A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain. Pain. 2015;156(12):2458-67.
- King SJ, Reid C, Forbes K, et al. A systematic review of oxycodone in the management of cancer pain. Palliat Med. 2011 Jul;25(5):454-70.
- Kivitz A, Ma C, Ahdieh H, et al. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. Clinical Therapeutics. 2006;38(3):352-64.
- Langford R, McKenna F, Ratcliffe S, et al. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. Arthritis & Rheumatism 2006;54(6):1829-37.
- Levorphanol prescribing information. Roxane Laboratories, Inc. Columbus, OH. September 2015.
- Ma K, Jiang W, Zhou Q, et al. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. Int J Clin Pract. 2008;62(2):241-7.
- Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2017;20(2S):S3-S92.
- *Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2013;11(128):31-42.*
- Mesgarpour B, Griebler U, Glechner A, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain. 2014;18(5):605-16.
- Melilli G, Samolsky Dekel BG, Frenquelli C, et al. Transdermal opioids for cancer pain control in patients with renal impairment. J Opioid Manag. 2014;10(2):85-93.
- Mercadante S, Porzio G, Ferrera P, et al. Low doses of transdermal fentanyl in opioid-naïve patients with cancer pain. Curr Med Research Opin. 2010;26(12):2765-8.
- Methadone oral solution prescribing information. Roxane Laboratories, Inc. Columbus, OH. March 2016.
- Methadose prescribing information. Mallinckrodt Inc. Hazelwood, MO. December 2016.
- Morley JS, Bridson J, Nash TP, et al. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliative Medicine. 2003;17:576-87.
- Morphabond prescribing information. Inspirion Delivery Technologies LLC. Valley Cottage, NY. October 2015.
- MS Contin prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Musclow SL, Bowers T, Vo H, et al. Long-acting morphine following hip or knee replacement: a randomized, double-blind and placebo-controlled trial (abstract). Pain Res Manag. 2012 Mar-Apr;17(2):83-8.
- National Institute on Drug Abuse (NIDA). What is the Federal Government Doing to Combat the Opioid Abuse Epidemic? May 1, 2015. Available at: http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2015/what-federal-government-doing-to-combat-opioid-abuse-epidemic. Accessed September 22, 2016.
- Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database Syst Rev. 2017;2:CD003971.
- Nucynta ER prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. December 2016.
- Office of Disease Prevention and Health Promotion. Pathways to Safer Opioid Use. October 6, 2015. Available at: http://health.gov/hcq/training-pathways.asp. Accessed March 22, 2017.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 21, 2017.
- OxyContin prescribing information. Purdue Pharma L.P. Stamford, CT. December 2016.
- Oxymorphone extended-release prescribing information. Mallinckrodt, Inc. Hazelwood, MO. November 2016.
- Park JH, Kim JH, Yun SC, et al. Evaluation of efficacy and safety of fentanyl transdermal patch (Duragesic D-TRANS) in chronic pain. Acta Neurochir. 2011;153:181-90.
- Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. Palliat Med. 2011 Jul;25(5):471-7.
- Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017. [Epub ahead of print]
- Quigley C. Hydromorphone for acute and chronic pain. Cochrane Database Syst Rev. 2002;(1):CD003447.
- Rauck RL, Nalamachu S, Wild JE, et al. Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: a randomized double-blind, placebo-controlled study. Pain Med. 2014 Feb [in press].
- Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011 Jan;27(1):151-62.
- Slatkin NE, Rhiner MI, Gould EM, et al. Long-term tolerability and effectiveness of oxymorphone extended release in patients with cancer (abstract). J Opioid Manag. 2010;6(3):181-91.
- Sloan P, Slatkin N, Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. Support Care Cancer. 2005;13:57-65.

- Summary of the Comprehensive Addiction and Recovery Act. American Society of Addiction Medicine (ASAM) Web site. http://www.asam.org/advocacy/issues/opioids/summary-of-the-comprehensive-addiction-and-recovery-act. Accessed September 20, 2016.
- US Department of Veterans Affairs. VA Accelerates Deployment of Nationwide Opioid Therapy Tool. March 9, 2015. Available at: http://www.va.gov/opa/pressrel/pressrelease.cfm?id=2681. Accessed March 22, 2017.
- Watson CPN, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003;105:71-8.
- Whittle SL, Richards BL, Husni E, et al. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011;(11):CD003113.
- Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain (review). Cochrane Database Syst Rev. 2013;(7):CD003868.
- Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract. 2010 Sept-Oct;10(5):416-27.
- Whittle SL, Richards BL, Husnit E, et al. Opioid therapy for treatment rheumatoid arthritis pain (review). Cochrane Database Syst Rev. 2011;(11):CD003113.
- Xartemis XR prescribing information. Mallinckrodt Brand Pharmaceuticals, Inc. Hazelwood, MO. March 2014.
- Xtampza ER prescribing information. Patheon Pharmaceuticals. Cincinnati, OH. December 2016.
- Zohydro ER prescribing information. Zogenix, Inc. San Diego, CA. December 2016.

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Therapeutic Class Overview
Antivirals, Influenza

INTRODUCTION

- Influenza is an infectious respiratory illness caused by the influenza A and influenza B viruses. Influenza epidemics occur annually in the United States, typically from late fall to early spring. Although the majority of infected individuals recover without complications, some cases of influenza result in severe illness or death *(Grohskopf et al 2016)*.
- The virus is primarily transmitted through direct contact large-particle respiratory droplets from an infected individual's coughs and sneezes. It is also spread through contact with surfaces contaminated by infected respiratory droplets. Adults begin to shed virus 1 day prior to symptom onset, and they remain contagious for 5 to 7 days after falling ill *(Centers for Disease Control and Prevention [CDC] 2016[a])*.
- Signs and symptoms of uncomplicated influenza illness include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Complications of influenza infection include sinusitis, otitis media, pneumonia, sepsis, and exacerbation of chronic medical conditions. Elderly adults, young children, pregnant women, and patients with chronic medical conditions have a higher risk of developing complications from influenza *(CDC 2016[b])*.
- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral prescription medications are also available for influenza prophylaxis and treatment; however, antiviral chemoprophylaxis is not a substitute for annual influenza vaccination *(Grohskopf et al 2016)*.
- Initiation of antiviral therapy to treat influenza is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at higher risk for influenza complications *(Fiore et al 2011)*.
- Two classes of antiviral medications are available and will be reviewed. The adamantanes include amantadine and Flumadine (rimantadine). The neuraminidase inhibitors include Rapivab (peramivir), Relenza (zanamivir), and Tamiflu (oseltamivir).
- Although the adamantanes are active against influenza A virus, resistance is high amongst currently circulating virus strains. The adamantanes lack activity against influenza B virus. Therefore, amantadine and rimantadine are not recommended for treatment or chemoprophylaxis during the current influenza season *(CDC 2017)*.
- The neuraminidase inhibitors are active against both influenza A and influenza B viruses. Rapivab (peramivir), Relenza (zanamivir), and oseltamivir are the only antivirals recommended for the current influenza season in the United States *(CDC 2017)*.
- Circulating influenza viruses are constantly evolving, and drug-resistant influenza virus strains have been reported. Prescribers should refer to influenza drug susceptibility patterns and treatment effects when selecting an antiviral agent *(CDC 2017)*.
- Medispan class: Antiparkinson, Dopaminergics and Influenza Agents. The only agent from the Antiparkinson, Dopaminergics category that will be included in this review is amantadine for the influenza indication.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine	✔
Flumadine (rimantadine)	✔
Rapivab (peramivir)	-
Relenza (zanamivir)	-
Tamiflu (oseltamivir)	✔

(*Drugs@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)
Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus	✔				
Prophylaxis and treatment of illness caused by various strains of influenza A virus in adults (17 years and older)		✔			
Prophylaxis against influenza A virus in children (1 to 16 years of age)		✔			
Treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days			✔		
Prophylaxis of influenza in adults and pediatric patients aged 5 years and older				✔	
Treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients aged 7 years and older who have been symptomatic for no more than 2 days				✔	
Prophylaxis of influenza A and B in patients 1 year and older					✔
Treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours					✔

[1] The changing of viruses over time is a limitation of use for antivirals. Emergence of resistance substitutions could decrease drug effectiveness. Other factors, such as changes in viral virulence, may also diminish clinical benefit of antivirals. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when selecting an antiviral.

[2] Amantadine is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.

[3] Limitations of use for Rapivab (peramivir):

- Efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.
- Efficacy could not be established in patients with serious influenza requiring hospitalization.

[4] Limitations of use for Relenza (zanamivir):

- Not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm.
- Has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- Has not been proven effective for prophylaxis of influenza in the nursing home setting.

[5] Limitations of use for Tamiflu (oseltamivir):

- Not recommended for patients with end-stage renal disease not undergoing dialysis.

(Prescribing information: amantadine capsules 2017, amantadine oral solution 2015, amantadine tablets 2017, Flumadine 2010, Rapivab 2016, Relenza 2016, Tamiflu 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adamantanes

- Clinical trials have demonstrated that the adamantanes are effective in both the prophylaxis and treatment of influenza A virus *(Bryson et al 1980, Crawford et al 1988, Dolin et al 1982, Hall et al 1987, Hayden et al 1989, Jackson et al 2011, Jefferson et al 2006[a], Jefferson et al 2006[b], Monto et al 1995, Reuman et al 1989)*.
- One systematic review assessed the efficacy and safety of adamantanes in healthy adults by analyzing 20 prophylaxis and 13 treatment randomized trials comparing amantadine or rimantadine with placebo. For prophylaxis, amantadine was 61% better than placebo at reducing influenza risk (P<0.001). Although rimantadine was 72% better than placebo at preventing influenza, statistical significance was not achieved. There was significant heterogeneity between the prophylaxis trials, and only a small sample size was available for rimantadine compared to amantadine. For treatment, amantadine and rimantadine both reduced the duration of fever by one day. Both agents caused gastrointestinal side effects, but amantadine caused significantly more adverse effects in the central nervous system than rimantadine *(Jefferson et al 2006[a])*.
- Influenza A virus resistance to amantadine and rimantadine has developed over the years. During the 2009 to 2010 influenza season, 100% of the 18 influenza H3N2 viruses tested in the United States were resistant to adamantanes. Similarly, 99.8% of the pandemic H1N1 viruses tested were resistant to adamantanes. Due to influenza A virus resistance and lack of activity against influenza B virus, the adamantanes are not recommended for the current influenza season *(CDC 2010[b], CDC 2017)*.

Neuraminidase inhibitors

- The neuraminidase inhibitors have demonstrated efficacy for their respective indications. Relenza (zanamivir) inhalation and oral oseltamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated a reduction in laboratory-confirmed influenza, illness, fever duration, secondary complications, and household contacts with influenza infection *(Aoki et al 2003, Chik et al 2004, Cooper et al 2003, Fry et al 2014, Halloran et al 2007, Hayden et al 1997, Hayden et al 1999, Hayden et al 2000, Hayden et al 2004, Hedrick et al 2000, Hiba et al 2011, Kaiser et al 2003, Kawai et al 2005, Kawai et al 2006, Lin et al 2006, MIST Study Group 1998, Monto et al 1999[a], Monto et al 1999[b], Monto et al 2002, Nicholson et al 2000, Peters et al 2001, Reuman et al 1989, Singh et al 2003, Treanor et al 2000, Turner et al 2003, Wang et al 2012, Welliver et al 2001, Whitley et al 2001)*.
- One systematic review analyzed 20 oseltamivir and 26 Relenza (zanamivir) randomized, placebo-controlled trials in order to better define their efficacy and safety. In prophylaxis trials, the risk of symptomatic influenza was reduced by 3.05% in patients treated with oseltamivir compared to placebo and 1.98% in patients treated with Relenza (zanamivir) compared to placebo. In adults, the time to first alleviation of symptoms was reduced by 0.7 days (P<0.0001) in patients receiving oseltamivir compared to placebo and 0.6 days (P<0.00001) in patients receiving Relenza (zanamivir) compared to placebo. Oseltamivir significantly reduced the time to alleviation of symptoms in non-asthmatic children and decreased the incidence of self-reported pneumonia. Relenza (zanamivir) significantly reduced the risk of bronchitis in adults with influenza. Neither treatment was a significant improvement over placebo in time to symptom alleviation in asthmatic children or risk of hospitalizations, otitis media, or sinusitis. Many studies included were at a high risk of selection bias due to inadequate reporting and a high risk of attrition bias due to selective reporting. All trials were sponsored by the manufacturers *(Jefferson et al 2014)*.
- Rapivab (peramivir) intravenous (IV) infusion is approved for the treatment of influenza A and B in adults. The primary endpoint for the main clinical trial supporting Food and Drug Administration (FDA)-approval of Rapivab (peramivir) was time to alleviation of symptoms. The trial evaluated 296 previously healthy adults presenting with the onset of influenza-like illness within the previous 48 hours and a positive influenza rapid antigen test. In this multicenter, double-blind, placebo-controlled clinical trial, patients were randomized to Rapivab (peramivir) 300 mg, 600 mg, or placebo as a single IV dose. Acetaminophen use was permitted. Patients self-reported body temperature, symptoms, and resumption of activities over 14 days. The primary endpoint, median time to alleviation of symptoms, was significantly earlier with Rapivab (peramivir) 300 mg (59.1 hours) and 600 mg (59.9 hours) compared to placebo (81.8 hours; both P=0.0092). There was no significant difference in the incidence of all adverse events in patients receiving Rapivab (peramivir)

compared to placebo. Diarrhea was the most common adverse event, occurring in 14.1%, 15.2% and 17% of the Rapivab (peramivir) 300 mg, 600 mg, and placebo groups, respectively *(Kohno et al 2010)*.

- Although studies have evaluated Rapivab (peramivir) in hospitalized patients and in children, both of these populations are not included in the FDA-approved labeling *(De Jong et al 2014, Ison et al 2014, Ison et al 2013, Sugaya et al 2012)*. The Phase 3 clinical trial of Rapivab (peramivir) in hospitalized influenza patients failed to meet its primary endpoint of reducing the time to clinical resolution compared to placebo. There are no clinical endpoints that have been validated for clinical trials of neuraminidase inhibitors treating hospitalized patients with influenza *(FDA 2014)*. In 2009, the United States issued an Emergency Use Authorization (EUA) program allowing Rapivab (peramivir) for the treatment of suspected or confirmed 2009 H1N1 influenza A virus infection in hospitalized patients *(Birnkrant and Cox 2009)*. Patients eligible for treatment were hospitalized, unable to tolerate or unresponsive to other available antivirals, or lacked a dependable oral or inhalation drug delivery route. The Public Health Emergency determination for the 2009 H1N1 influenza pandemic expired on June 23, 2010 *(CDC 2010[a])*.
- Numerous placebo-controlled trials have demonstrated the efficacy of neuraminidase inhibitors individually, but head-to-head trials directly comparing the agents are limited. One randomized, double-blind, placebo-controlled safety trial compared the use of oseltamivir, Relenza (zanamivir), and placebo in 390 healthy adults for influenza chemoprophylaxis over 16 weeks. The study showed that both treatments were well tolerated compared to placebo, and there were no discontinuations due to adverse events *(Anekthananon et al 2013)*.
- A Phase 3 multinational, multicenter, double-blind, randomized, noninferiority trial compared a single dose of 300 or 600 mg IV Rapivab (peramivir) to 5 days of oral oseltamivir in 1,091 patients with seasonal influenza. The primary endpoint, time to alleviation of influenza symptoms, had a median of 78.0 hours in patients receiving 300 mg of Rapivab (peramivir), 81.0 hours in patients receiving 600 mg of Rapivab (peramivir), and 81.8 hours in patients receiving oseltamivir. Both strengths of Rapivab (peramivir) were noninferior to oseltamivir with a noninferiority margin of 0.170. There was no significant difference between treatments in the incidence of complications of influenza infection *(Kohno et al 2011)*.
- Observational studies comparing the clinical efficacy of Rapivab (peramivir), Relenza (zanamivir), and oseltamivir in treating influenza have demonstrated within-class variation in the time to alleviation of influenza symptoms. The lack of robust data from randomized, head-to-head trials prevents the recommendation of one neuraminidase inhibitor over another. Local and seasonal susceptibility trends, route of administration, and patient-specific factors such as age and compliance should be taken into account when selecting an agent for antiviral drug therapy *(Kawai et al 2008, Takemoto et al 2013)*.
- While influenza virus strains resistant to specific neuraminidase inhibitors have emerged, overall resistance remains low. According to surveillance data on seasonal influenza virus strains, the rate of resistance to oseltamivir is 1 to 3% and resistance to Relenza (zanamivir) is less than 1% *(Li et al 2015)*.

CLINICAL GUIDELINES

- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All individuals six months of age and older should receive an influenza vaccination each year, unless contraindicated. The live attenuated intranasal influenza vaccine is not recommended during the 2016 to 2017 influenza season due to low effectiveness. Prophylactic antiviral administration is not a substitute for early influenza vaccination *(Grohskopf et al 2016)*.
- Amantadine and rimantadine are not recommended for antiviral treatment or prophylaxis of influenza A virus strains in the United States due to high rates of resistance *(American Academy of Pediatrics [AAP] 2016, Fiore et al 2011, CDC 2017)*.
- The antivirals recommended by the CDC for the current influenza season include oseltamivir, Relenza (zanamivir) and Rapivab (peramivir). Routine or widespread use of antivirals for chemoprophylaxis is not recommended due to concerns for viral resistance. Oseltamivir and Relenza (zanamivir) are recommended for post-exposure prophylaxis in patients who are severely immunosuppressed and in patients at a high risk for influenza complications who are either not a candidate for vaccination or received their annual vaccination less than 2 weeks prior to exposure *(CDC 2017)*.
- Treatment of influenza with antiviral therapy is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at a high risk for complications *(CDC 2017)*.
- Populations at a high risk for influenza complications and recommended to receive antiviral treatment include children younger than 2 years old, adults age 65 and above, pregnant or postpartum women, American Indians, Alaska Natives,

obese patients with a body mass index (BMI) of 40 kg/m² and above, patients younger than 19 years old receiving long-term treatment with aspirin, residents of nursing homes, and patients with immunosuppression, chronic disorders (eg, pulmonary, cardiovascular, renal, hepatic, hematological and metabolic), or neurologic conditions *(CDC 2017)*.

- Antiviral therapy works best when administered within 48 hours of symptom onset. Treatment initiation should not be delayed for the results of diagnostic testing. Early administration of antivirals may shorten the duration of fever, reduce the risk of influenza-related complications such as otitis media and pneumonia, reduce death in hospitalized patients, and decrease the duration of hospitalization in hospitalized children *(CDC 2017)*.

SAFETY SUMMARY

- Common adverse events with adamantanes include headache, anorexia, dry mouth, and agitation.
- Amantadine and rimantadine should be used with caution in patients with epilepsy due to an increased risk for seizures.
- Amantadine has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. There have also been reports of death from overdose and suicide attempts with amantadine.
- Common adverse events with neuraminidase inhibitors include nausea, vomiting, and headache. The most common adverse effect with Rapivab (peramivir) is diarrhea.
- All three neuraminidase inhibitors have labelled warnings for neuropsychiatric events such as hallucinations and delirium. Patients should be monitored for signs of abnormal behavior.
- Oseltamivir and Rapivab (peramivir) have warnings for serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome.
- Relenza (zanamivir) has a warning for bronchospasm and should not be used in patients with asthma or chronic obstructive pulmonary disease. It is also contraindicated in patients with milk protein allergies.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Capsules, oral solution, tablets	Oral	Once daily or twice daily Adults: 200 mg once daily or 100 mg twice daily Pediatric patients: 1 to 9 years: 4.4 to 8.8 mg/kg/day not to exceed 150 mg per day 9 to 12 years: 100 mg twice daily The safety and efficacy of amantadine in newborn infants and infants below the age of 1 year have not been established.	Should be taken for 10 days following a known exposure. If using in conjunction with vaccine until antibody response, then take for 2 to 4 weeks. Treatment of illness should be started within 24 to 48 hours of symptom onset and continued for 24 to 48 hours after symptoms disappear. For adult patients intolerant to 200 mg daily dose because of central nervous system or other toxicities: 100 mg daily dose Because amantadine is primarily excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals who are 65

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age or older according to the following: For CrCl=30 to 50 mL/min: 200 mg 1st day, then 100 mg daily For CrCl=15 to 29 mL/min: 200 mg 1st day, then 100 mg on alternate days For CrCl<15 mL/min and HD: 200 mg every 7 days For patients ≥65 years: 100 mg once daily The dose of amantadine may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.
Flumadine (rimantadine)	Tablets	Oral	Twice daily **Adults** Treatment: 100 mg twice daily for 7 days Prophylaxis: 100 mg twice daily **Pediatric patients** Prophylaxis in patients 1 to 9 years: 5 mg/kg/day, not to exceed 150 mg per day 10 to 16 years: Refer to the adult dose	Treatment of illness should be started within 48 hours of symptoms. A suspension can be made from the tablets and is stable for 14 days. Dose adjustment in patients ≥65 years: 100 mg once daily Dose adjustment in patients with CrCl<29 mL/min: 100 mg daily Dose adjustment in patients with severe hepatic dysfunction: 100 mg daily
Rapivab (peramivir)	Injection	IV	One time (within 2 days of onset of influenza symptoms)	A single dose administered by IV infusion for a minimum of 15 minutes. Dose adjustment in patients with CrCl=30 to 49 mL/min: 200 mg Dose adjustment in patients with CrCl=10 to 29 mL/min: 100 mg HD: Administer after dialysis
Relenza (zanamivir)	Inhalation powder (in blisters)	Oral inhalation	Once daily or twice daily, depending on the indication	The 10-mg dose is provided by 2 inhalations (one 5-mg blister

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
		via Diskhaler device	Treatment (≥7 years): 10 mg twice daily for 5 days Prophylaxis in household setting (≥5 years): 10 mg once daily for 10 days Prophylaxis in community outbreak (adults and adolescents): 10 mg once daily for 28 days	per inhalation). Patients scheduled to use an inhaled bronchodilator at the same time as Relenza should use their bronchodilator before taking Relenza. If Relenza is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional. Due to the low systemic bioavailability of Relenza following oral inhalation, no dosage adjustments are necessary in patients with renal Impairment; however, the potential for drug accumulation should be considered.
Tamiflu (oseltamivir)	Capsules, powder for oral suspension	Oral	Once daily or twice daily, depending on the indication **Patients ≥13 years** Treatment: 75 mg twice daily for 5 days Prophylaxis: 75 mg once daily for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, may be continued for up to 12 weeks. **Patients <13 years** Treatment: • 2 weeks to <1 year: 3 mg/kg twice daily for 5 days • 1 to 12 years: 30 to 75 mg twice daily for 5 days Prophylaxis: • 1 to 12 years: 30 to 75 mg once daily for 10 days. During a community	Start treatment within 48 hours of symptom onset or close contact with infected individual. Taking with food may enhance tolerability. In an emergency, a suspension can be made from capsules. Dosage adjustment is recommended for patients with a CrCl between 10 and 60 mL/minute and for patients with ESRD undergoing routine HD or CAPD. Not recommended for patients with ESRD not undergoing dialysis. No dosage adjustment for mild to moderate hepatic impairment. Safety not evaluated in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			outbreak, can continue for up to six weeks (or up to 12 weeks in immuno-compromised patients).	

CAPD=continuous ambulatory peritoneal dialysis; CrCl =creatinine clearance; ESRD=end stage renal disease; HD=hemodialysis
*See the current prescribing information for full details

CONCLUSION

- The first line of protection against influenza is vaccination. All individuals six months of age and older without contraindications should receive yearly influenza vaccination *(AAP 2016, Fiore et al 2011, Grohskopf et al 2016)*.
- Antivirals are available for the prevention and treatment of influenza. Overall, the adamantanes and neuraminidase inhibitors have demonstrated safety and efficacy for their respective indications. However, amantadine and rimantadine are not currently recommended due to high rates of resistance in circulating influenza virus strains *(CDC 2017)*.
- Relenza (zanamivir) and oseltamivir are both effective in preventing influenza but are not substitutes for annual vaccination. They are recommended as post-exposure chemoprophylaxis in patients with a high risk for influenza complications who are not sufficiently protected by vaccination *(Fiore et al 2011, CDC 2017, Harper et al 2009, Panel on Opportunistic Infections 2013)*. Rapivab (peramivir) is not approved or recommended for influenza prophylaxis *(CDC 2017)*.
- Rapivab (peramivir), Relenza (zanamivir), and oseltamivir effectively treat influenza by reducing the duration of fever and illness. Initiation of treatment is recommended as soon as possible for patients with suspected influenza who are hospitalized, severely ill, or at high risk for influenza complications *(Fiore et al 2011, AAP 2016, CDC 2017, Harper et al 2009, Panel on Opportunistic Infections 2013)*.
- Limited within-class comparisons prevent the recommendation of one neuraminidase inhibitor over another. Factors to consider when selecting an antiviral agent include the route of administration, seasonal and geographical susceptibility trends, and patient-specific factors such as age and compliance *(Takemoto et al 2013)*.
- The most common adverse events with amantadine and rimantadine are headache, anorexia, dry mouth, and agitation. The adamantanes are associated with an increased risk for seizures.
- The most common adverse events with Relenza (zanamivir) and oseltamivir are headache, nausea, and vomiting. Diarrhea is the most common adverse event with Rapivab (peramivir). The neuraminidase inhibitors have a labelled warning for neuropsychiatric events such as delirium and abnormal behavior leading to injury.

REFERENCES

- Amantadine capsules [package insert], Parsippany, NJ: Actavis Pharma, Inc.; January 2017.
- Amantadine oral solution [package insert], Farmville, NC: CMP Pharm, Inc.; January 2015.
- Amantadine tablets [package insert], Parsippany, NJ: Actavis Pharma, Inc.; January 2017.
- American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2016–2017. *Pediatrics*. 2016;138(4):e20162527.
- Anekthananon T, Pukritayakamee S, Ratanasuwan W, et al. Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: a randomized, double-blind, placebo-controlled safety trial over 16 weeks. *J Antimicrob Chemother*. 2013;68(3): 697–707.
- Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment: IMPACT trial. *J Antimicrob Chemother*. 2003;51(1):123-9.
- Birnkrant D, Cox E. The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza. *N Engl J Med*. 2009;361(23):2204-2207.
- Bryson YJ, Monahan C, Pollack M, Shields WD. A prospective double-blind study of side effects associated with the administration of amantadine for influenza A virus prophylaxis. *J Infect Dis*. 1980;141(5):543-7.
- Centers for Disease Control and Prevention. Clinical Signs and Symptoms of Influenza. Updated May 26, 2016[a]. https://www.cdc.gov/flu/professionals/acip/clinical.htm. Accessed May 2, 2017.
- Centers for Disease Control and Prevention. Flu Symptoms & Complications. Updated May 23, 2016[b]. https://www.cdc.gov/flu/about/disease/complications.htm. Accessed May 2, 2017.
- Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. Updated March 8, 2017. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed May 2, 2017.
- Centers for Disease Control and Prevention. Termination of Declaration of Emergency Justifying Emergency Use Authorization (EUA) of Certain Antiviral Drugs – Zanamivir, Oseltamivir Phosphate and Peramivir. June 21, 2010[a]. http://www.cdc.gov/H1N1flu/EUA/pdf/Antivirals.pdf. Accessed May 2, 2017.
- Centers for Disease Control and Prevention. Update: influenza activity - United States, 2009-10 season. *MMWR*. 2010[b]; 59(29):901-8.

- Chik KW, Li CK, Chan PK, et al. Oseltamivir prophylaxis during the influenza season in a pediatric cancer centre: prospective observational study. *Hong Kong Med J*. 2004;10(2):103-6.
- Cooper NJ, Sutton AJ, Abrams KR, et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomized controlled trials. *BMJ*. 2003;326(7401):1235.
- Crawford SA, Clover RD, Abell TD, et al. Rimantadine prophylaxis in children: a follow-up study. *Pediatr Infect Dis J*. 1988;7(6):379-83.
- De Jong MD, Ison MG, Monto AS, et al. Evaluation of Intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Inf Dis*. 2014;59(15 December):e172-e185.
- Dolin R, Reichman RC, Madore HP, et al. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med*. 1982;307(10):580-4.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 2, 2017.
- Fiore AE, Frye A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* Recomm Rep. 2011;60(1):1-24.
- Flumadine [package insert], Detroit, MI: Caraco Pharmaceutical Laboratories, Ltd.; April 2010.
- Food and Drug Administration. Center for Drug Evaluation and Research. New Drug Application – 206426Orig1s000. Peramivir Medical Review. Food and Drug Administration. August 22, 2014. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206426Orig1s000MedR.pdf. Accessed May 2, 2017.
- Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomized placebo-controlled trial. *Lancet Infect Dis*. 2014;14(2):109-118.
- Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2016–17 Influenza Season. August 26, 2016. MMWR. 2016; 65(5);1–54. http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm. Accessed May 2, 2017.
- Hall CB, Dolin R, Gala CL, et al. Children with influenza A infection: treatment with rimantadine. *Pediatrics*. 1987;80(2):275-82.
- Halloran ME, Hayden FG, Yang Y, et al. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am J Epidemiol*. 2007;165(2):212-21.
- Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children-diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(8):1003-32.
- Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J of Med*. 1999;341(18):1336-43.
- Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post exposure prophylaxis. *J Infect Dis*. 2004;189(3):440-9.
- Hayden FG, Belshe RB, Clover RD, et al. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med*. 1989;321(25):1696-702.
- Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. *N Engl J Med*. 2000;343(18):1282-9.
- Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. *N Engl J Med*. 1997;337(13):874-80.
- Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J*. 2000;19(5):410-7.
- Hiba V, Chowers M, Levi-Vinograd I, et al. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study. *J Antimicrob Chemother*. 2011;66:1150-5.
- Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. *Antivir Ther*. 2014;19(4):349-61.
- Ison MG, Hui DS, Clezy K, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized patients. *Antivir Ther*. 2013;19:651-661.
- Jackson RJ, Cooper KL, Tappenden P, et al. Oseltamivir, zanamivir and amantadine in the prevention of influenza: a systematic review. *J Infect*. 2011;62:14-25.
- Jefferson T, Demicheli V, Di Pietrantonj C, et al. Amantadine and rimantadine for influenza A in adults. *Cochrane Database Syst Rev*. 2006[a];(2):CD001169.
- Jefferson T, Demicheli V, Rivetti D, et al. Antivirals for influenza in healthy adults: systematic review. *Lancet*. 2006[b];367(9507):303-13.
- Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review). *Cochrane Database Syst Rev*. 2014;4: CD008965.
- Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*. 2003;163(14):1667-72.
- Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. *Clin Infect Dis*. 2006;43(4):439-44.
- Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect*. 2008;56(1):51-7.
- Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. *Clin Infect Dis*. 2005;40(9):1309-16.
- Kohno S, Kida H, Mizuguchi M, et al. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2010;54(11):4568-4574.
- Kohno S, Yen MY, Cheong HJ, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2011;55(11):5267-76.
- Li TC, Chan MC, Lee N. Clinical implications of antiviral resistance in influenza. *Viruses*. 2015;7(9):4929-44.

- Lin JT, Yu XZ, Cui DJ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Curr Med Res Opin*. 2006;22(1):75-82.
- MIST Study Group. Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. 1998;352(9144):1877-81.
- Monto A, Ohmit SE, Hornbuckle K, et al. Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother*. 1995;39(10):2224-8.
- Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis*. 1999[a];180(2):254-61.
- Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis*. 2002;186(11):1582-8.
- Monto AS, Robinson DP, Herlocher ML, et al. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA*. 1999[b];282(1):31-5.
- Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of influenza: a randomized controlled trial. *Lancet*. 2000;355(9218):1845-50.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 2, 2017.
- Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Department of Health and Human Services. Updated November 6, 2013. https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed May 2, 2017.
- Peters PH Jr, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc*. 2001;49(8):1025-31.
- Rapivab [package insert], Durham, NC: BioCryst Pharmaceuticals, Inc.; August 2016.
- Relenza [package insert], Research Triangle Park, NC: GlaxoSmithKline LLC; August 2016.
- Reuman PD, Bernstein DI, Keefer MC, et al. Efficacy and safety of low dosage amantadine hydrochloride as prophylaxis for influenza A. *Antiviral Res*. 1989;11(1):27-40.
- Singh S, Barghoorn J, Bagdonas A, et al. Clinical benefits with oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. *Clin Drug Investig*. 2003;23(9):561-9.
- Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. *Antimicrob Agents Chemother*. 2012;56(1):369–377.
- Takemoto Y, Asai T, Ikezoe I, et al. Clinical effects of oseltamivir, zanamivir, laninamivir and peramivir on seasonal influenza infection in outpatients in Japan during the winter of 2012-2013. *Chemotherapy*. 2013;59(5):373-8.
- Tamiflu [package insert], South San Francisco, CA: Genentech, Inc.; June 2016.
- Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *JAMA*. 2000;283(8):1016-24.
- Turner D, Wailoo A, Nicholson K, et al. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. *Health Technol Assess*. 2003;7(35):iii-iv, xi-xiii, 1-170.
- Wang K, Shun-Shin M, Gill P, et al. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev*. 2012;4:CD002744.
- Welliver R, Monto A, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts. *JAMA*. 2001;285(6):748-54.
- Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20(2):127-33.

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Therapeutic Class Overview
Fluoroquinolones

INTRODUCTION

- The fluoroquinolones are broad-spectrum antibiotics grouped into generations based on their spectrum of activity (Bolon, 2011).
  - First generation agents, which are structurally quinolones rather than fluoroquinolones, possess activity against aerobic gram-negative bacteria but are not effective against aerobic gram-positive bacteria or anaerobes.
    - The first generation agents (eg, nalidixic acid, cinoxacin) are no longer on the market.
  - Second generation agents, the original fluoroquinolones, contain a fluorine atom at position C-6. These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage.
    - The available second generation fluoroquinolones include ciprofloxacin, levofloxacin, and ofloxacin. Lomefloxacin and norfloxacin are second generation agents which are no longer on the market.
  - Third generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, and also possess good activity against anaerobes.
    - All three of the third generation agents, gatifloxacin, grepafloxacin, and sparfloxacin, were removed from the market due to toxicities.
  - Fourth generation fluoroquinolones have superior coverage against pneumococci and anaerobes. These agents include moxifloxacin and gemifloxacin. One additional agent, trovafloxacin, was removed from the market due to toxicities.
  - The most recently approved fluoroquinolone, delafloxacin, has an even broader spectrum of antibiotic activity and is commonly referred to as a “next generation” fluoroquinolone.
- The fluoroquinolones have been used to treat a variety of infections including urinary tract infections, sinusitis, lower respiratory tract infections, intra-abdominal infections, infectious diarrhea, skin and skin structure infections, sexually transmitted diseases, and bacterial prostatitis. A few of the agents also have Food and Drug Administration (FDA) approval for inhalational anthrax and plague. There is also considerable off-label data for use in neutropenic patients and for treatment of tuberculosis and mycobacteria infections in patients with human immunodeficiency virus (HIV). Due to the boxed warning for disabling and potentially irreversible serious adverse reactions involving the tendons, muscles, joints, nerves, and central nervous system, fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (FDA press release, 2016).
- As with all antibiotics, local resistance patterns should be considered when prescribing these agents.
- Ciprofloxacin, delafloxacin, levofloxacin, and moxifloxacin are available as intravenous and oral formulations. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in otic and/or ophthalmic formulations. Only the oral formulations and indications will be included in this review.
- Medispan class: Fluoroquinolones

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Avelox (moxifloxacin)	✔
Baxdela (delafloxacin)	-
Cipro (ciprofloxacin)	✔
ciprofloxacin extended release*	✔
Factive (gemifloxacin)	-
Levaquin (levofloxacin)	✔
ofloxacin†	✔

* The branded product, Cipro XR, is no longer marketed.
† The branded product, Floxin, is no longer marketed.
(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Avelox (moxifloxacin)	BAXDELA (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.	✔ ∞		✔ ∞			✔ ∞	
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae* or *H. influenzae.*							✔ ∞
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus, or M. catarrhalis.*	✔ ∞				✔ ‡ ∞	✔ ǂ ∞	
Community acquired pneumonia caused by *S. pneumoniae* or *H. influenzae.*							✔
Community acquired pneumonia caused by *S. pneumoniae**, *H. influenzae*, *M. catarrhalis,* methicillin-susceptible *S. aureus, K. pneumoniae, Mycoplasma pneumoniae, or Chlamydia pneumoniae.*	✔				✔ ‡‡	✔ ∫	
Lower respiratory tract infections caused *by Escherichia coli, K. pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, H. influenzae, H. parainfluenzae*, or penicillin-susceptible *S. pneumoniae*.** Also, *M. catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.			✔				
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes.*	✔					✔	
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus*, *S. pyogenes,* or *P. mirabilis.*							✔
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, E. coli, K. pneumoniae, or E. cloacae.*	✔						
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, S. pyogenes, Enterococcus faecalis,* or *P. mirabilis.*						✔	
Skin and skin structure infections caused by *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, methicillin-resistant and methicillin-susceptible *S. aureus*, *S. haemolyticus*, *S. lugdunensis*, *S. agalactiae*, *S. anginosus* Group, *S. pyogenes*, and *E. faecalis*		✔					
Skin and skin structure infections caused by *E. coli, K. pneumoniae, E. cloacae, P. mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, P. aeruginosa*, methicillin-susceptible *S. aureus*, methicillin-susceptible *Staphylococcus epidermidis,* or *S. pyogenes.*			✔				
Bone and joint infections caused by *E. cloacae, Serratia marcescens*, or *P. aeruginosa*.			✔				
Complicated intra-abdominal infections caused by *E. coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, E. faecalis, P. mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron,* or	✔						

Indication	Avelox (moxifloxacin)	BAXDELA (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Peptostreptococcus species.							
Complicated intra-abdominal infections (used in combination with metronidazole) caused by *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae*, or *B. fragilis*.			✔				
Uncomplicated urinary tract infection (acute cystitis) caused by *E. coli, P. mirabilis, E. faecalis,* or *Staphylococcus saprophyticus.*				✔ ∞			
Uncomplicated urinary tract infection caused by *E. coli, K. pneumoniae,* or *S. saprophyticus.*						✔ ∞	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, E. faecalis,* or *P. aeruginosa.*				✔		✔ ǂǂ	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, P. aeruginosa, or Citrobacter diversus.*							✔
Acute uncomplicated pyelonephritis caused by *E. coli.*				✔		✔	
Urinary tract infection caused by *E. coli, K. pneumoniae, E. cloacae, Serratia marcescens, P. mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter koseri* (*diversus*), *Citrobacter freundii, P. aeruginosa,* methicillin-susceptible *S. epidermidis, S. saprophyticus,* or vancomycin-susceptible *E. faecalis*.			✔ †				
Acute uncomplicated cystitis in females caused by *E. coli* or *S. saprophyticus*.			✔ ∞				
Acute uncomplicated cystitis caused by *C.diversus, Enterobacter aerogenes, E. coli, K. pneumoniae, P. mirabilis,* or *P. aeruginosa.*							✔ ∞
Chronic bacterial prostatitis caused *by E. coli* or *P. mirabilis.*			✔				
Chronic bacterial prostatitis caused *by E. coli, E. faecalis* or methicillin-susceptible *S. epidermidis.*						✔	
Prostatitis caused by *E. coli.*							✔
Infectious diarrhea caused by *E. coli* (enterotoxigenic isolates), *Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei*.			✔				
Typhoid fever (enteric fever) caused by *Salmonella typhi*.			✔				
Uncomplicated cervical and urethral gonorrhea caused by *Neisseria gonorrhoeae*.			✔				✔
Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.			✔ ††			✔	
Plague caused by *Yersinia pestis* (treatment and prophylaxis).	✔		✔ ††			✔	
Urethritis and cervicitis caused by *Chlamydia trachomatis*							✔
Mixed infections of the urethra and cervix or pelvic inflammatory disease due to *N. gonorrhoeae and C. trachomatis.*							✔

* Multi-drug resistant isolates

[∫] Also indicated for *H. parainfluenzae* and *Legionella pneumophilia*. Also indicated for nosocomial pneumonia caused by methicillin-susceptible *S. aureus*, *P. aeruginosa*, *S. marcescens, E. coli, K. pneumoniae, H. influenzae*, or *S. pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *P. aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.
[‡] Not indicated for *K. pneumoniae* or methicillin-susceptible *S. aureus.*
[‡‡] Not indicated for methicillin-susceptible *S. aureus.*
[ǂ] Not indicated for *K. pneumoniae*.
[ǂǂ] Also indicated for *E. cloacae.*
[**] Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *S. pneumoniae.*
[†] Complicated urinary tract infections and pyelonephritis due to *E. coli* for children one to 17 years but not drug of first choice.
[††] For adults and children
∞ Reserve for use in patients who have no alternative treatment options.

(Prescribing information: Avelox, 2016; Baxdela, 2017; Cipro, 2016; Ciprofloxacin extended release tablet, 2016; Factive, 2016; Levaquin, 2017; Ofloxacin, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of the fluoroquinolones has been well documented in the treatment of genitourinary, respiratory, dermatological, and other miscellaneous infections, including typhoid fever and complicated intra-abdominal infections.
- A meta-analysis demonstrated no significant differences in clinical or microbiological efficacy between the quinolones for the treatment of acute cystitis (Rafalsky et al, 2006). Another meta-analysis found no difference between fluoroquinolones and other classes of antibiotics for uncomplicated cystitis with regard to symptomatic cure (Zalmanovici-Trestioreanu et al, 2010). For the treatment of urinary tract infections, two randomized clinical trials were conducted that directly compared the once-daily, extended-release formulation of ciprofloxacin with the equivalent dose of the twice-daily immediate release formulation (Fourcroy et al, 2005; Talan et al, 2004). Overall, the extended-release formulation was found to provide comparable bacteriological eradication rates and/or clinical cure rates as the immediate-release formulation with comparable rates of adverse reactions.
- Several head-to-head trials have demonstrated no significant differences between fluoroquinolone agents for the treatment of urinary tract infections (Arredondo-Garcia et al, 2004; Auquer et al, 2002; Peterson et al, 2008; Raz et al, 2000; Richard et al, 2008; Schaeffer et al, 1992). In one study, cefpodoxime did not demonstrate non-inferiority versus ciprofloxacin in the treatment of acute cystitis (Hooten et al, 2012).
- Both levofloxacin and ciprofloxacin have demonstrated efficacy in the treatment of bacterial prostatitis (Bundrick et al, 2003; Naber et al, 2008). In a meta-analysis, no fluoroquinolone demonstrated consistent superiority over another for the treatment of chronic bacterial prostatitis (Perletti et al, 2013).
- Four meta-analyses have been conducted comparing quinolones to other antibiotics for the treatment of acute sinusitis and community-acquired pneumonia (Karageorgopoulos et al, 2008; Salkind et al, 2002; Varadakas et al, 2008; Raz-Pasteur et al, 2015). Results from these analyses established the efficacy of the quinolones in respiratory infections. When compared to other antibiotics (β-lactams, macrolides, β-lactams/macrolide combination therapy, doxycycline, or a ketolide), treatment with quinolones was generally clinically comparable or superior. However, the majority of trials assessed in the meta-analysis by Salkind et al included sparfloxacin, trovafloxacin, and grepafloxacin, which are not currently available in the United States. In another meta-analysis, gemifloxacin was shown to have a higher treatment success rate than other fluoroquinolones and similar rates to β-lactams and macrolides in the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis (Zhang et al, 2012). Eradication rates were similar between gemifloxacin and other fluoroquinolones, β-lactams, and macrolides.
- A meta-analysis in patients with acute COPD exacerbations did not find a consistent significant benefit of antibiotics across outcomes with the exception of patients admitted to the intensive care unit (Vollenweider et al, 2012).
- For patients with skin and skin structure infections, two trials demonstrated similar clinical success and eradication rates with levofloxacin and ciprofloxacin (Nichols et al, 1997; Nicodemo et al, 1998). Additionally, results from clinical trials

have revealed similar cure rates for delafloxacin compared to tigecycline, linezolid, and the combination of vancomycin/aztreonam in the treatment of acute bacterial skin and skin structure infections (O'Riordan et al 2015; Kingsley et al, 2016; O'Riordan et al, 2016).

- A meta-analysis of four randomized, controlled trials evaluated moxifloxacin versus other combination antibiotic regimens for the treatment of intra-abdominal infections (Mu et al, 2012). This analysis showed that moxifloxacin had similar clinical cure rates, bacteriological success rates, and mortality compared with those of the control group.

CLINICAL GUIDELINES

- Treatment guidelines for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis recommend fluoroquinolones as alternative agents (Berbari et al, 2015; Chow et al, 2012; Gupta et al, 2011; Mandell et al, 2007; Snellman et al, 2013; Stevens et al, 2014).
- Fluoroquinolones should be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea (Guerrant et al, 2001; Stern et al, 2008).
- The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms. They are not recommended for routine use in pelvic inflammatory disease unless antimicrobial susceptibility testing is performed and the fluoroquinolone will be administered in combination with metronidazole (CDC, 2015).

SAFETY SUMMARY

- All fluoroquinolones carry a boxed warning for disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly observed adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion).
  - The risk for fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants.
- Due to the potentially permanent serious adverse events involving the tendons, muscles, joints, nerves, and central nervous system, the FDA published a safety communication which recommends reserving the use of fluoroquinolones in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections for patients with no alternative treatment options (FDA press release, 2016). A subsequent safety alert released by the FDA stated that after review, it did not find that use of fluoroquinolones resulted in detached retina, aortic aneurysm, or aortic dissection (FDA press release, 2017).
- Fluoroquinolones may cause QT interval prolongation, anaphylactic reactions, phototoxicity, *Clostridium difficile* diarrhea, blood glucose disturbances. Additionally, fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis and should therefore be avoided.
- The most common adverse events with fluoroquinolones include gastrointestinal (eg, nausea, vomiting, diarrhea) and central nervous system (eg, dizziness, headache) toxicities. Rash is frequently observed with fluoroquinolones and is especially common with gemifloxacin.
- All fluoroquinolones bind to multivalent cations. Administration of a fluoroquinolone should be separated by at least two hours from products containing aluminum, magnesium, iron, or zinc.
- Additional drug interactions include Class IA and Class III antiarrhythmics, nonsteroidal anti-inflammatory drugs, phenytoin, probenecid, sulfonylureas, theophylline, tizanidine, and warfarin.
- Oral dosing of ciprofloxacin, gemifloxacin, levofloxacin, and ofloxacin should be adjusted in renal impairment. Delafloxacin is not recommended for use in patients with end stage renal disease. The daily dose of ofloxacin should not exceed 400 mg in patients with severe liver dysfunction.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Avelox (moxifloxacin)*,†	Tablet	Oral	Every 24 hours	
Baxdela (delafloxacin)*	Tablet	Oral	Every 12 hours	Not recommended in ESRD (eGFR <

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				15 including hemodialysis)
Cipro (ciprofloxacin)*,†	Tablet, suspension	Oral	Every 12 hours	Oral dose adjustments are recommended in renal impairment. Ofloxacin dose should not exceed 400 mg per day in patients with severe liver dysfunction disorders.
ciprofloxacin extended release	Tablet	Oral	Every 24 hours	
Factive (gemifloxacin)	Tablet	Oral	Every 24 hours	
Levaquin (levofloxacin)* ,†	Tablet, oral solution	Oral	Every 24 hours	
ofloxacin†	Tablet	Oral	Every 12 hours	

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease
* Also available as intravenous solution
† Also available as otic and/or ophthalmic formulations
See the current prescribing information for full details

CONCLUSION

- Fluoroquinolones have a broad spectrum of activity and may be used to treat a variety of infections. Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy appears comparable among agents. No fluoroquinolone has consistently demonstrated superiority over another.
- Fluoroquinolones should be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea (Stern et al, 2008; Guerrant et al, 2001).
  - Treatment guidelines recommend fluoroquinolones as alternative agents for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis (Berberi et al, 2015; Gupta et al, 2011; Mandell et al, 2007; Solomkin et al, 2010; Stevens et al, 2014). They are not generally recommended for the treatment of bacterial sinusitis (Chow et al, 2012; Snellman et al, 2013). The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms (CDC, 2015).
- All fluoroquinolones share a boxed warning for disabling and potentially irreversible serious adverse reactions such as tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion). Due to the risk for permanent adverse effects, the FDA warns that fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (FDA press release, 2016).
- Additional warnings for the class include QT prolongation, blood glucose disturbances, *Clostridium difficile*-associated diarrhea, and phototoxicity. Fluoroquinolones should be avoided in patients with a history of myasthenia gravis.

REFERENCES

- Arredondo-Garcia JL, Figueroa-Damian R, Rosas A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. J Antimicrob Chemother. 2004;54(4):840-3.
- Auquer F, Cordon F, Gorina E, et al; the Urinary Tract Infection Study Group. Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. Clin Microbiol Infect. 2002;8(1):50-4.
- Avelox prescribing information. Bayer HealthCare Pharmaceuticals, Inc. Whippany, NJ. September 2016.
- Baxdela prescribing information. Melinta Therapeutics. Lincolnshire, IL. June 2017.
- Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015 September:e26-e46. Available from http://cid.oxfordjournals.org/content/61/6/e26.full.pdf+html. Accessed June 6, 2017.
- Bolon MK. The newer fluoroquinolones. Med Clin N Am. 2011; 95: 793–817.
- Bundrick W, Heron SP, Ray P, et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double-blind multicenter study. Urology. 2003 Sep;62(3):537-41.
- Centers for Disease Control and Prevention (CDC). Plague: Resources for Clinicians. 2015. (content on the internet). Available from http://www.cdc.gov/plague/healthcare/clinicians.html. Accessed June 6, 2017.
- Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. Available from: http://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed June 6, 2017.
- Chow AW, Benninger MS, Brook I, et al. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. Clin Infect Dis. 2012 May:e1-e41. Available from https://www.idsociety.org/uploadedFiles/IDSA/Guidelines-

Patient_Care/PDF_Library/IDSA%20Clinical%20Practice%20Guideline%20for%20Acute%20Bacterial%20Rhinosinusitis%20in%20Children%20and%20Adults.pdf. Accessed June 6, 2017.
- Cipro prescribing information. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ. September 2016.
- Ciprofloxacin extended release tablet prescribing information. Mylan Pharmaceuticals Inc. Morgantown, WV. August 2016.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 5, 2017.
- Factive prescribing information. Merus Labs. Toronto, ON, Canada. May 2016.
- Food and Drug Administration (FDA) Drug Safety Communication. FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. [press release]. July 26, 2016 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm. Accessed June 6, 2017.
- Food and Drug Administration (FDA) Drug Safety Communication. Fluoroquinolone antibacterial drugs for systemic use: drug safety communication – warnings updated due to disabling side effects. [press release]. May 10, 2017. Available at: https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm513065.htm. Accessed June 5, 2017.
- Fourcroy JL, Berner B, Chiang YK, et al. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother. 2005;49(10):4137-43.
- Guerrant RL, Van Gilder T, Steiner TS, et al; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331-51.
- Gupta K, Hooton TM, Naber KG, et al.; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar;52(5):e103-20.
- Hooten TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis. A randomized trial. JAMA. 2012;307(6):583-5-89.
- Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with β-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. CMAJ. 2008;178(7):845-54.
- Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. J Antimicrob Chemother. 2016;71(3):821-829.
- Levaquin prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. February 2017.
- Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
- Mu YP, Liu RL, Wang LQ, et al. Moxifloxacin monotherapy for treatment of complicated intra-abdominal infections: a meta-analysis of randomised controlled trials. Int J Clin Pract. 2012 Feb;66(2): 210–17.
- Naber KG, Roscher K, Botto H, et al. Oral levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis. Int J Antimicrob Agents. 2008;32:145-53.
- Nichols RL, Smith JW, Gentry LO, et al. Multicenter, randomized study comparing levofloxacin and ciprofloxacin for uncomplicated skin and skin structure infections. South Med J. 1997;90(12):1193-200.
- Nicodemo AC, Robledo JA, Jasovich A et al. A multicenter, double-blind, randomized study comparing the efficacy and safety of oral levofloxacin versus ciprofloxacin in the treatment of uncomplicated skin and skin structure infections. Int J Clin Pract. 1998;52(2):69-74.
- O'Riordan W, McManus A, Teras J, et al. A global phase 3 study of delafloxacin compared to vancomycin/aztreonam in patients with acute bacterial skin and skin structure infections. Open Forum Infect Dis. 2016;3(Suppl 1):1347.
- O'Riordan W, Mehra P, Manos P, et al. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. Int J Infect Dis. 2015;30:67-73.
- Ofloxacin prescribing information. Larken Laboratories. Canton, MS. July 2016.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 5, 2017.
- Perletti G, Marras E, Wagenlehner FME, et al. Antimicrobial therapy for chronic bacterial prostatitis. Cochrane Database Syst Rev. 2013;8:CD009071.
- Peterson J, Kaul S, Khashab M, et al. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology. 2008;71(1):17-22.
- Rafalsky V, Andreeva I, Rjabkova E. Quinolones for uncomplicated acute cystitis in women. Cochrane Database Syst Rev. 2006 Jul 19;3:CD003597.
- Raz R, Naber KG, Raizenberg C, et al. Ciprofloxacin 250 mg twice daily versus ofloxacin 200 mg twice daily in the treatment of complicated urinary tract infections in women. Eur J Clin Microbiol Infect Dis. 2000;19(5):327-31.
- Raz-Pasteur A, Shasha D, Paul M. Fluoroquinolones or macrolides alone versus combined with β-lactams for adults with community-acquired pneumonia: Systematic review and meta-analysis. Int J Antimicrob Agents. 2015;46(3):242-8.
- Richard GA, Klimberg IN, Fowler CL, et al. Levofloxacin versus ciprofloxacin versus lomefloxacin in acute pyelonephritis. Urology. 1998;52(1):51-5.
- Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis. Ann Pharmacother. 2002;36(12):1938-43.
- Schaeffer AJ, Anderson RU. Efficacy and tolerability of norfloxacin vs ciprofloxacin in complicated urinary tract infection. Urology. 1992;40(5):446-9.
- Snellman L, Adams W, Anderson G, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Respiratory Illness in Children and Adults. Update 2013 January. Available at https://www.icsi.org/_asset/1wp8x2/RespIllness.pdf. Accessed June 6, 2017.
- Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010 Feb;11(1):79-109.
- Stern EJ, Uhde KB, Shadomy SV, et al. Conference report on public health and clinical guidelines for anthrax [conference summary]. Emerg Infect Dis [serial on the Internet]. 2008 Apr. Available from http://wwwnc.cdc.gov/eid/article/14/4/07-0969.htm. Accessed June 6, 2017.
- Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-e52.

- Talan DA, Klimberg IW, Nicolle LE, et al. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol. 2004;171(2 Pt 1):734-9.
- Varadakas KZ, Siempos II, Grammatikos A, et al. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ. 2008;179(12):1269-77.
- Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease (review). Cochrane Database Syst Rev. 2012;12:CD010257.
- Zalmanovici-Trestioreanu A, Green H, Paul M, et al. Antimicrobial agents for treatment uncomplicated urinary tract infection in women (review). Cochrane Database Syst Rev. 2010;10:CD007182.
- Zhang L, Wang R, Matthew FE, et al. Gemifloxacin for the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis: a meta-analysis of randomized controlled trials. Chin Med J. 2012;125(4): 687-95 .

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Therapeutic Class Overview
Epinephrine Products for Anaphylaxis

INTRODUCTION

- Anaphylaxis, a potentially fatal disorder, is a severe, acute, multisystem syndrome with rapid onset resulting from a sudden release of mast cell- and basophil-derived mediators into circulation. Most commonly, it results from immunologic reactions to foods, medications, and insect stings. In humans, the heart, vasculature system, and lungs are predominately affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest (American Heart Association, 2005; Sicherer, 2017).
- Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized, and is the treatment of choice because the benefits associated with epinephrine are greater than any other available pharmacologic intervention (e.g., antihistamines, bronchodilators, glucocorticoids). Epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from alpha-1 (α1), beta-1 (β1), and beta-2 (β2) adrenergic receptor agonist effects and include increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2), and decreased release of mediators of inflammation from mast cells and basophils (β2) (Campbell et al, 2014; Sicherer, 2017).
- In general, pharmacologic treatment of anaphylaxis is based upon extrapolation from therapies utilized in cardiac arrest and asthma, uncontrolled clinical trials with humans who develop anaphylaxis during insect sting challenges, randomized controlled trials of interventions such as epinephrine in people not experiencing anaphylaxis at the time of administration, and animal anaphylaxis models. Randomized, placebo-controlled trials that meet current standards have not been performed for any pharmacologic intervention in humans experiencing anaphylaxis. Of note, placebo-controlled trials with epinephrine will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration.
- The epinephrine products for anaphylaxis (ADRENACLICK®, AUVI-Q®, EPIPEN®, EPIPEN JR®, and authorized generics of ADRENACLICK, EPIPEN, and EPIPEN JR) are all Food and Drug Administration (FDA) approved for the emergency treatment of severe allergic reactions. All agents are available as single use, auto-injectors to be administered as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh. Based on clinical trial data, intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine (American Heart Association, 2005; Simons et al, 2001; Simons et al, 1998).
- These agents are intended for immediate administration in patients with a history of anaphylactic reaction, and prompt prehospital epinephrine injection is associated with a lower risk of hospitalization and fatality. Furthermore, these agents are designed for emergency supportive therapy and are not intended to substitute immediate medical care. In conjunction with the administration of one of these agents, patients should seek appropriate medical care (Sicherer, 2017).
- Each agent is available as a 0.15 and 0.3 mg injection, and differences among the various agents are minimal and include specific packaging and administration requirements. Based on a comparison of package inserts, a notable difference between the products is that only ADRENACLICK and its' authorized generics' needles are exposed after the injection. Furthermore, AUVI-Q is the first epinephrine auto-injector with audio instructions that directs patients and caregivers through the injection process. AUVI-Q was voluntarily recalled in 2015 due to reports of device malfunctions, and was re-launched with manufacturing modifications in February 2017 (DRUGS@FDA, 2017; FDA recall press release, 2015; Kaléo Pharmaceuticals press release, 2016; Tirrell, 2017).
- Medispan class: Anaphylaxis Therapy Agent

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ADRENACLICK (epinephrine injection)*	Amreda Pharmaceuticals, Impax Generics	05/30/2003	✓†
AUVI-Q (epinephrine injection) ‡	Kaléo Pharmaceuticals	08/10/2012	-
EPIPEN (epinephrine injection)	Mylan	12/22/1987	✓†
EPIPEN JR (epinephrine injection)			

*ADRENACLICK brand is currently not marketed.
† Authorized generics are available for all strengths. All generics are rated as "BX" and are not considered to be therapeutically equivalent by the FDA due to insufficient data.
‡ Kaléo Pharmaceuticals relaunched AUVI-Q in February 2017.

(Drugs@FDA, 2017; FDA Listing of Authorized Generics, 2017; Kaléo Pharmaceuticals press release, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Epinephrine
Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis	✔

(Prescribing information: ADRENACLICK, 2016; AUVI-Q, 2016; epinephrine, 2016; EPIPEN, 2016; EPIPEN JR, 2016)

CLINICAL EFFICACY SUMMARY

- A thorough literature search failed to retrieve any clinical trials evaluating the epinephrine products for anaphylaxis in their FDA-approved indications. It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can kill within minutes and mandates prompt epinephrine administration. As noted in the FDA-approved package labeling of the various agents, epinephrine is essential for the treatment of anaphylaxis.
- Epinephrine is the recognized treatment of choice for severe allergic reactions and anaphylaxis, as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts (American Academy of Allergy, Asthma and Immunology [AAAAI] Board of Directors, 1998; Boyce et al, 2011; Fineman et al, 2015; Campbell et al, 2014; Golden et al, 2017; Kemp, 2008; Lieberman et al, 2015; National Institute of Allergy and Infectious Diseases, 2010; Sampson et al, 2014; Sicherer, 2017; Simons et al, 1998; Simons et al, 2001; Simons et al, 2011; Simons et al, 2012; Simons et al, 2013; Simons et al, 2015).
- It is recommended that patients who have a history of anaphylaxis or systemic reaction to allergens, including insect stings or foods, should be given a prescription for an injectable epinephrine device and be advised to carry it with them at all times (Boyce et al, 2011; Golden et al, 2017; Sampson et al, 2014).

SAFETY SUMMARY

- There are no absolute contraindications to the use of the epinephrine products for anaphylaxis in a life-threatening allergic reaction.
- Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be administered.
- Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.
- Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by *Clostridia* (gas gangrene) have been reported at the injection site following epinephrine injection for anaphylaxis. To decrease the risk of Clostridium infection, do not inject the drug into the buttock. Should signs and symptoms of infection occur, patients should seek medical care.
- Epinephrine is not intended as a substitute for immediate medical care; in conjunction with its administration, patients should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.
- Epinephrine should only be injected into the anterolateral aspect of the thigh. In children, the leg should be held firmly in place prior to and during injection to reduce injury, as lacerations, bent needles, embedded needles, and other injuries have been observed after epinephrine auto-injector administration on children. Avoid accidental injection into the hands or feet as this may result in loss of blood flow to the area. Furthermore, epinephrine should not be injected into the buttock. If an accidental injection occurs, patients should inform a health care provider when he/she goes to the nearest emergency room for further treatment of anaphylaxis.
    - An analysis evaluated 22 cases of epinephrine auto-injector-related injuries including lacerations and embedded needles in children. In response, product warnings were updated to require immobilization of a child's leg prior to and during injection, and injection time for the EPIPEN and EPIPEN JR was reduced from 10 to 3 seconds (Brown et al, 2016).
- Possible inadvertent intravascular administration should also be avoided.
- Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations. Epinephrine auto-injectors, ADRENACLICK, and AUVI-Q contain sodium bisulfite; whereas, EPIPEN and EPIPEN JR contain sodium metabisulfite. Thus, all forms of epinephrine used for anaphylaxis contain sulfites that may cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. Because the alternatives to epinephrine in a life-threatening situation may not be satisfactory, the presence of a sulfite should not deter administration of the agent for the treatment of serious allergic or other emergency situations, even in a sulfite-sensitive patient.
- Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache, and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Large doses of epinephrine can cause acute hypertension. Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute, life-threatening allergic reaction.
- Several drug-drug interactions exist with epinephrine. Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines. The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs. Ergot alkaloids may also reverse the pressor effects of epinephrine.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
Epinephrine*	Injection: 0.15 mg/0.15 mL (AUVI-Q, epinephrine) 0.15 mg/0.3 mL (epinephrine, EPIPEN JR) 0.3 mg/0.3 mL (AUVI-Q, epinephrine, EPIPEN)	Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis: Injection: 0.15 mg (15 to 30 kg) or 0.3 mg (≥30 kg)	Self-administered auto-injectors that deliver a single dose of either strength. Injection should be administered into the anterolateral aspect of the thigh, through clothing if necessary. Administration time varies by device (i.e., 5 seconds for AUVI-Q; 3 seconds for EPIPEN, EPIPEN JR, and authorized generic; and 10 seconds for ADRENACLICK authorized generic). In conjunction with its administration, patients should seek appropriate medical care. Any remaining volume that is left after administration cannot be further administered and should be discarded with the device. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

Note: All productions only available in a two pack containing two auto-injectors.
*ADRENACLICK brand currently not marketed.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Epinephrine	No dosage adjustment required in the elderly.	No dosage adjustment required in children.*	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category C** Unknown whether excreted in breast milk; use with caution.

*Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary.
** Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into the circulation.
- Foods, medications, and insect stings that cause a subsequent immunologic reaction are the most common reason for an anaphylactic reaction to occur. In humans, the heart, vasculature system and lungs are predominantly affected during anaphylaxis, and fatalities can result from circulatory collapse and respiratory arrest. Guidelines recommend prompt epinephrine injection for sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in a patient (American Heart Association, 2005; Sicherer, 2017).
- Epinephrine can be life-saving when administered as rapidly as possible once anaphylaxis is recognized, and is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts (AAAAI Board of Directors, 1998; Boyce et al, 2011; Campbell et al, 2014; Fineman et al, 2015; Golden et al, 2017; Kemp et al, 2008; Lieberman et al, 2015; National Institute of Allergy and Infectious Diseases, 2010; Sampson et al, 2014; Sicherer, 2017; Simons et al, 1998; Simons et al, 2001; Simons et al, 2011; Simons et al, 2012; Simons et al, 2013; Simons et al, 2015).
- Acting as an agonist at α1, β1 and β2 adrenergic receptors, epinephrine works in the emergency treatment of anaphylaxis by causing increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2) and decreased release of mediators of inflammation from mast cells and basophils (β2). Of note, clinical trials evaluating epinephrine for emergency anaphylaxis treatment will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration (Song et al, 2014).
- Included in this review are the epinephrine products for anaphylaxis which are all FDA-approved for the emergency treatment of severe allergic reactions. As noted in their FDA-approved package labeling, epinephrine is essential for the treatment of anaphylaxis, and these agents are designed for emergency supportive therapy. They are not intended to substitute immediate medical care; in conjunction with the administration of one of these agents, patients should seek appropriate medical care.
- All of the epinephrine products for anaphylaxis are available as single use, auto-injectors to be administered, by the patient or caregiver, as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh.
- Differences among the various epinephrine agents are minimal and include specific packaging and administration requirements. AUVI-Q is the only epinephrine auto-injector that contains audio instructions to guide patients and caregivers through the injection process. Each agent is available as a 0.15 and 0.3 mg injection, and authorized generics are available within the class.

REFERENCES

- ADRENACLICK prescribing information. Amedra Pharmaceuticals LLC; Horsham, PA. May 2016.
- American Academy of Allergy, Asthma and Immunology (AAAAI) Board of Directors. Anaphylaxis in schools and other childcare settings. J Allergy Clin Immunol. 1998;102(2):173-6.
- American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Part 10.6: Anaphylaxis. Circulation. 2005;000:IV-143-IV-145.
- Brown JC, Tuuri RE, Akhter S, et al. Embedded Needles Caused by Epinephrine Autoinjector Use in Children. Ann Emerg Med. 2016 Mar;67(3):307-315.e8. doi: 10.1016/j.annemergmed.2015.07.011.
- AUVI-Q prescribing information. Kaleo, Inc.; Richmond, VA. May 2016.
- Boyce JA, Assaad A, Burks AW, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. Nutrition Research. 2011; 31:61-75.
- Campbell RL, Li JT, Nicklas RA, et al and Joint Task Force on Practice Parameters. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol. 2014;113:599-608.
- DRUGS@FDA.com [database on the internet]. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm Accessed March 23, 2017.
- Epinephrine prescribing information. Impax Generics; Hayward, CA. July 2016.
- EPIPEN, EPIPEN JR prescribing information. Meridian Medical Technologies; Columbia, MD. May 2016.
- FDA Listing of Authorized Generics. Authorized generics. 2017. Available at: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm126391.htm. Accessed March 23, 2017.
- FDA recall press release. Auvi-Q (epinephrine injection, USP): Recall – Potential inaccurate dosage delivery. October 29, 2015. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm470010.htm. Accessed March 23, 2017.
- Fineman S, Bowman S, Campbell R, et al; for the American College of Allergy, Asthma & Immunology (in press). Addressing barriers to emergency anaphylaxis care: from emergency medical services to emergency department to outpatient follow-up. Ann Allergy Asthma Immunol. 2015 Oct;115(4):301-5.

- Golden DB, Demain J, Freeman T, et al. Stinging insect hypersensitivity: A practice parameter update 2016. Ann Allergy Asthma Immunol. 2017 Jan;118(1):28-54. doi: 10.1016/j.anai.2016.10.031.
- Kaléo Pharmaceuticals Press Release. Kaléo Announces 2017 U.S. Return Of Auvi-Q® (Epinephrine Injection, USP) Auto-Injector For Life-Threatening Allergic Reactions. Available at: https://kaleopharma.com/kaleo-announces-2017-u-s-return-of-auvi-q-epinephrine-injection-usp-auto-injector-for-life-threatening-allergic-reactions/. Accessed March 24, 2017.
- Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis-a statement of the world allergy organization. World Allergy Organ J. 2008 Jul;1(7 Suppl):S18-26. doi: 10.1097/WOX.0b013e31817c9338.
- Lieberman P, Nicklas RA, Randolph C, et al. The diagnosis and management of anaphylaxis practice parameter: 2015 update. Annals of Allergy, Asthma & Immunology. 2015;115(5):341-384.
- National Institute of Allergy and Infectious Diseases: Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010). Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm . Accessed March 23, 2017.
- Sampson HA, Aceves S, Bock A, et al for the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology. Food allergy: a practice parameter update – 2014. J Allergy Clin Immunol. 2014 Nov;134(5):1016-25.e43.
- Sicherer SH, Simons FE. Section on allergy and immunology. Epinephrine for first-aid management of anaphylaxis. Pediatrics. 2017 Mar;139(3). pii: e20164006. doi: 10.1542/peds.2016-4006.
- Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 1998;101(1 pt 1):33.
- Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular vs subcutaneous injection. J Allergy Clin Immunol. 2001;108(5):871.
- Simons FER, Ardusso LRF, Bilo MB, et al. World Allergy Organization Guidelines for the assessment and management of anaphylaxis. World Allergy Organization Journal. 2011 Feb; 4:13-37.
- Simons FER, Ardusso LF, Bilo MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol. 2012;12:389-99.
- Simons FER, Ardusso LF, Dimov V, et al. 2013 Update of the Evidence Base: World Allergy Organization Anaphylaxis Guidelines. Int Arch Allergy Immunol. 2013;162:193-204.
- Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8(1):32.
- Song TT, Worm M, and Lieberman P, et al. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. Allergy. 2014;69:983-91.
- Tirrell M. EpiPen gets a new rival: Auvi-Q. Available at: http://finance.yahoo.com/news/epipen-competitor-auvi-q-comes-182139050.html. 2017. Accessed March 24, 2017.

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Therapeutic Class Overview
Immunomodulators

INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (Choy et al, 2001). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved five originator TNF inhibitors: CIMZIA® (certolizumab), ENBREL® (etanercept), HUMIRA® (adalimumab), REMICADE® (infliximab), and SIMPONI®/SIMPONI® ARIA™ (golimumab), as well as three biosimilar TNF inhibitors: AMJEVITA (adalimumab-atto), ERELZI (etanercept-szzs), and INFLECTRA (infliximab-dyyb). Other agents targeting different cells and cytokines are also FDA approved for RA treatment. These include ORENCIA® (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; RITUXAN® (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; ACTEMRA® (tocilizumab), which has activity directed against the IL-6 receptor; and KINERET® (anakinra), which targets the IL-1 receptor. An oral agent on the market, XELJANZ® and XELJANZ® XR (tofacitinib), targets Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include ILARIS® (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and ENTYVIO™ (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. OTEZLA® (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and STELARA (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; STELARA is additionally indicated for the treatment of CD. COSENTYX™ (secukinumab) and TALTZ® (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO; COSENTYX is additionally indicated to treat PsA and AS. A related agent, SILIQ™ (brodalumab), is an IL-17 receptor antagonist indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - ILARIS for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - KINERET for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
- RITUXAN is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). These indications will not be discussed in this review.
- TYSABRI® (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (TYSABRI prescribing information, 2016). ARCALYST (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (ARCALYST prescribing information, 2016).
- Although FDA approved, the launch plans for AMJEVITA (adalimumab-atto) and ERELZI (etanercept-szzs) are pending and may be delayed; thus, information on AMJEVITA and ERELZI is not currently included in this review.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar or Generic Availability	Type of Agent
ACTEMRA (tocilizumab)	Genentech	01/08/2010	-	Human monoclonal antibody targeting the IL-6 receptor
CIMZIA (certolizumab)	UCB	04/22/2008	-	TNFα inhibitor
COSENTYX (secukinumab)	Novartis	01/21/2015	-	Human monoclonal antibody to IL-17A
ENBREL (etanercept)	Amgen	11/02/1998	-*	sTNFR fusion protein, TNFα inhibitor
ENTYVIO (vedolizumab)	Takeda Pharmaceuticals America, Inc.	05/20/2014	-	Human monoclonal antibody binds to the α4β7 integrin
HUMIRA (adalimumab)	Abbott	12/31/2002	-*	TNFα inhibitor
ILARIS (canakinumab)	Novartis	06/17/2009	-	Human monoclonal antibody that binds to IL-1ß
INFLECTRA (infliximab-dyyb)	Celltrion/ Hospira/Pfizer	04/05/2016	N/A†	TNFα inhibitor
KINERET (anakinra)	Swedish Orphan Biovitrum	11/14/2001	-	IL-1 receptor antagonist
ORENCIA (abatacept)	Bristol Myers Squibb	12/23/2005	-	sCTLA-4-Ig recombinant fusion protein
OTEZLA (apremilast)	Celgene Corporation	03/21/2014	-	Small-molecule phosphodiesterase 4 inhibitor
REMICADE (infliximab)	Janssen Biotech	8/24/1998	-†	TNFα inhibitor
RITUXAN (rituximab)	Genentech	11/26/1997	-	Anti-CD20 monoclonal antibody
SILIQ (brodalumab)‡	Valeant	02/15/2017	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
SIMPONI/ SIMPONI ARIA (golimumab)	Janssen Biotech	04/24/2009 and 07/18/2013	-	TNFα inhibitor
STELARA (ustekinumab)	Janssen Biotech	09/25/2009	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
TALTZ (ixekizumab)	Eli Lilly	03/22/2016	-	Human monoclonal antibody to IL-17A
XELJANZ / XELJANZ XR (tofacitinib)	Pfizer	11/06/2012 and 02/23/2016	-	Small molecule Janus kinase (JAK) inhibitor

*ERELZI (etanercept-szzs) and AMJEVITA (adalimumab-atto) have been FDA approved as biosimilars to ENBREL (etanercept) and HUMIRA (adalimumab), respectively. The specific launch dates for these products are pending and may be delayed. Further information on ERELZI and AMJEVITA will be included in this review closer to the time of launch.
†INFLECTRA (infliximab-dyyb) has been FDA approved as a biosimilar to REMICADE (infliximab). It is not an interchangeable biologic.
‡SILIQ is anticipated to be launched in the second half of 2017.

(Drugs@FDA, 2016; Prescribing information: ACTEMRA, 2016; CIMZIA, 2017; COSENTYX, 2016; ENBREL, 2016; ENTYVIO, 2014; HUMIRA, 2016; ILARIS, 2016; INFLECTRA, 2016; KINERET, 2016; ORENCIA, 2016; OTEZLA, 2015; REMICADE, 2015; RITUXAN, 2014; SILIQ, 2017; SIMPONI, 2017; SIMPONI ARIA, 2017; STELARA, 2016; TALTZ, 2016; XELJANZ/XELJANZ XR, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: CAPS, FMF, HIDS/MKD, and TRAPS)

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
ACTEMRA (tocilizumab)	✔ *		✔ **	✔ **						
CIMZIA (certolizumab)	✔	✔				✔	✔			
COSENTYX (secukinumab)					✔ ‡	✔	✔			
ENBREL (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
ENTYVIO (vedolizumab)		✔						✔		
HUMIRA (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔	✔ ▼

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
ILARIS" (canakinumab)			✔ **							
INFLECTRA (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
KINERET▼▼ (anakinra)	✔ ∞									
ORENCIA (abatacept)	✔ ∞∞			✔ ⌂						
OTEZLA (apremilast)					✔ ‡	✔				
REMICADE (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
RITUXAN‴ (rituximab)	✔ ⧺									

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
SILIQ (brodalumab)					✓‡‡					
SIMPONI (golimumab)	✓†					✓††	✓	✓~		
SIMPONI ARIA (golimumab)	✓†									
STELARA (ustekinumab)		✓⌐⌐⌐			✓‡	✓				
TALTZ (ixekizumab)					✓‡					
XELJANZ / XELJANZ XR (tofacitinib)	✓‡‡									

*Patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of ENBREL, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.

‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼Treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
▼▼KINERET is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
"ILARIS also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 6 years and old with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.
⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with one or more TNF blockers
⊥In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
⊥⊥For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (REMICADE only). The biosimilar INFLECTRA did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
"'RITUXAN also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA).
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to one or more TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┤ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┤┤ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of ORENCIA (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (Genovese et al, 2011).
- ORENCIA (abatacept), REMICADE (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (N=431). Enrolled patients had had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after six months of treatment, some differences in favor of abatacept were evident after one year of treatment. After one year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (Schiff et al, 2008).
- Treatment with ORENCIA (abatacept) was directly compared to treatment with HUMIRA (adalimumab), both added to MTX, in a multicenter, investigator-blind, randomized controlled trial (N=646) of RA patients with inadequate response to MTX. After two years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the two groups after two years of treatment. Rates of AEs were similar between treatment groups (Schiff et al, 2014).
- The RAPID-1 and RAPID-2 studies compared CIMZIA (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (Keystone et al, 2008; Smolen et al, 2009a). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks zero, two, and four then 200 or 400 mg every two weeks attained greater ACR 20, ACR 50 and ACR 70 responses over patients on placebo and MTX, respectively, after 24 weeks (P≤0.01). The response rates were sustained with active treatment over 52 weeks (Keystone et al, 2008). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (Keystone et al, 2008; Smolen et al, 2009a). A trial evaluated CIMZIA (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least one prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; P<0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (Fleischmann et al, 2009).
- ievedCIMZIA (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, P≤0.05) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least six months (Smolen et al, 2015a).
- A randomized, double-blind, placebo-controlled trial (N=316) conducted in Japan compared CIMZIA (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (Atsumi et al, 2016). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; P<0.001). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population.
- The FDA approval of SIMPONI (golimumab) for RA was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients greater than or equal to18 years of age with moderate to severe active disease. A greater percentage of patients from all three trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (Emery et al, 2009; Keystone et al, 2009; Smolen et al, 2009b). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (Keystone et al, 2009; Smolen et al, 2009b). Response with golimumab + MTX was sustained for up to five years (Keystone et al, 2013a; Smolen et al, 2015b).

- SIMPONI ARIA (golimumab) was studied in patients with RA. In one trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; P<0.001) (Kremer et al, 2010). In the GO-FURTHER trial (N=592), golimumab 2 mg/kg IV or placebo was given at weeks zero, four and then every eight weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [P<0.001]) (Weinblatt et al, 2013). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (Bingham et al, 2015). In the GO-MORE trial, investigators treated patients with golimumab SQ for six months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ+IV group and the SQ golimumab group (Combe et al, 2014).
- The efficacy and safety of ACTEMRA (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients ages 18 years and older with active RA. Patients were diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was given every four weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to tumor necrosis factor (TNF) antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (Emery et al, 2008; Genovese et al, 2008; Jones et al, 2010; Kremer et al, 2011; Smolen et al, 2008).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al, 2010).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had three times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at six months as compared to MTX (33% vs 4%), and these rates continued to increase over time to one year (47% vs 8%) (Kremer et al, 2011). These benefits were maintained or improved at two years with no increased side effects (Fleishmann et al, 2013).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every four weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with less than 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (P<0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (P<0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg) (Smolen et al, 2008).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated

with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; P value not reported) (Genovese et al, 2008).
    - RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists was randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with HUMIRA (adalimumab) and REMICADE (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al, 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (Gabay et al, 2013).
- More recently, results of a randomized, double-blind trial evaluating ACTEMRA (tocilizumab) in early RA were published (Bijlsma et al, 2016). Patients (N=317) had been diagnosed with RA within one year, were DMARD-naïve, and had a DAS28 score of ≥2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 <2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P<0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P=0.06 for tocilizumab plus MTX vs MTX; P=0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the subcutaneous formulation of ACTEMRA (tocilizumab) was based on one multicenter, double-blind, randomized, controlled trial in patients (N=1,262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every four weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (Burmester et al, 2014a). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (Burmester et al, 2016). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ ACTEMRA administered every other week (Kivitz et al, 2014).
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the XELJANZ (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (Fleishmann et al, 2012). In another Phase 3 study, XELJANZ (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to HUMIRA (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (van Vollenhoven et al, 2012). The ORAL Scan trial showed the ACR 20 response rates at month six for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo (P<0.0001 for both comparisons) (van der Heijde et al, 2013). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; P<0.001) (Lee et al, 2014). No radiographic progression was defined as a change from baseline in the modified total Sharp score of <0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.
- In the ORAL Step study, patients with RA who had an inadequate response to one or more TNF inhibitors were randomized to XELJANZ (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (Burmester et al, 2013a; Strand et al, 2015a). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5

mg (41.7%; 95% CI, 6.06 to 28.41; P=0.0024) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; P<0.0001) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; P<0.0001) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; P<0.0001) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.

- INFLECTRA (infliximab-dyyb) was evaluated and compared to REMICADE (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the REMICADE and INFLECTRA groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the two products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (N=302) through 102 weeks, all patients received INFLECTRA. Response rates were maintained, with no differences between the INFLECTRA maintenance group and the group who switched from REMICADE to INFLECTRA.
- Two studies, one double-blind and one open-label, evaluated RITUXAN (rituximab) in patients who had failed treatment with a TNF blocker (Cohen et al, 2006, Haraoui et al, 2011). All patients continued to receive MTX. Both studies showed greater than 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (Lopez-Olivo et al, 2015) examined RITUXAN (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.
- In the open-label ORBIT study (N=295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either RITUXAN (rituximab) (n=144) or a TNF inhibitor (physician/patient choice of ENBREL [etanercept] or HUMIRA [adalimumab]; n=151) (Porter et al, 2016). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (Gottenberg et al, 2016). Patients (N=300) were randomized to receive a second TNF inhibitor (n=150) or a non-TNF-targeted biologic (n=150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included HUMIRA (adalimumab), ENBREL (etanercept), CIMZIA (certolizumab), and REMICADE (infliximab), and the non-TNF biologics included ACTEMRA (tocilizumab), RITUXAN (rituximab), and ORENCIA (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of >1.2 points resulting in a score of ≤3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (P=0.003 or P=0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (P=0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-

TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.

- Another recent randomized trial (Manders et al, 2015) evaluated the use of ORENCIA (abatacept) (n=43), RITUXAN (rituximab) (n=46), or a different TNF inhibitor (n=50) in patients (N=139) with active RA despite previous TNF inhibitor treatment. ACTEMRA (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined ORENCIA (abatacept) for the treatment of RA. ACR 50 response was not significantly different at three months but was significantly higher in the abatacept group at six and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (Maxwell et al, 2009).
- The safety and efficacy of HUMIRA (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses at six months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (Navarro-Sarabia et al, 2005). In another study, patients received adalimumab 20 mg or 40 mg every other week for one year, and then could receive 40 mg every other week for an additional nine years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (Keystone et al, 2013b).
- A Phase 3, open-label study evaluated the long-term efficacy of HUMIRA (adalimumab) for RA. Patients receiving adalimumab in one of four early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (Furst et al, 2015).
- A Cochrane review was performed to compare KINERET (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (Mertens et al, 2009).
- In another Cochrane review, ENBREL (etanercept) was compared to MTX or placebo in adult patients with RA and found that at six months 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (Blumenauer et al, 2003). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (O'Dell et al, 2013).
- A more recent Cochrane review (Singh et al, 2016a) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included XELJANZ (tofacitinib) and 9 biologics (ORENCIA [abatacept], HUMIRA [adalimumab], KINERET [anakinra], CIMZIA [certolizumab], ENBREL [etanercept], SIMPONI [golimumab], REMICADE [infliximab], RITUXAN [rituximab], and ACTEMRA [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS <1.6 or DAS28 <2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.

- Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
- Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.

- A similar Cochrane review focused on the use of biologic or XELJANZ (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (Singh et al, 2016b). A total of 41 randomized trials (N=14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or XELJANZ (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (Singh et al, 2017). The review included 12 randomized trials (N=3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- Another recent Cochrane review (Hazlewood et al, 2016) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or XELJANZ (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effects was small.
- A meta-analysis evaluated the efficacy of REMICADE (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (Wiens et al, 2009).
- Another meta-analysis of randomized controlled trials included HUMIRA (adalimumab), KINERET (anakinra), ENBREL (etanercept), and REMICADE (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; P<0.05) (Nixon et al, 2007).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (Donahue et al, 2012). They concluded that there is limited head to head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of two biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- s for the FDA approval of STELARA ,927) evaluated the efficacy of withdrawing biologics from patients with RA who in sustained remission or had low disease activity (Galvao et al, 2016). The biologics in the identified trials were TNF inhibitors, most commonly ENBREL (etanercept) or HUMIRA (adalimumab). Compared to withdrawing the

medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA-approval of HUMIRA (adalimumab) for the treatment of AS was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; P<0.001). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients (P<0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (P<0.001) (van der Heijde et al, 2006).
- In two double-blind, randomized, placebo-controlled trials, the efficacy of ENBREL (etanercept) was evaluated in patients with AS (Calin et al, 2004; Gorman et al, 2002). Etanercept had a significantly greater response to treatment compared to placebo (P<0.001)(Gorman et al, 2002). More patients achieved an ASAS 20 response compared to placebo (P<0.001)(Calin et al, 2004). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (Davis et al, 2008). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 (P<0.0001). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (P<0.0001 for both) (Braun et al, 2011).
- The FDA-approval of SIMPONI (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least three months (N=356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (Inman et al, 2008). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to five years in an open-label extension trial (Deodhar et al, 2015). Safety profile through five years was consistent with other TNF inhibitors.
- The efficacy of REMICADE (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (P<0.0001)(Braun et al, 2002), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group (P<0.001)(van der Heijde et al, 2005).
- INFLECTRA (infliximab-dyyb) was evaluated alongside REMICADE (infliximab; European Union formulation) for the treatment of AS in PLANETAS (N=250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between INFLECTRA and REMICADE. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the REMICADE and INFLECTRA groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (N=174) through 102 weeks, all patients received INFLECTRA. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of CIMZIA (certolizumab) for the treatment of AS was established in one randomized, double-blind, placebo-controlled study (N=325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every two weeks and certolizumab 400 mg every four weeks compared to placebo at 12

weeks (Landewe et at, 2014). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (Sieper et al, 2015a). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (Sieper et al, 2015b).

- The efficacy and safety of COSENTYX (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (Baeten et al, 2015). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, P<0.001 for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group (P<0.001 for secukinumab 150 mg vs placebo; P=0.10 for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52.
- In two systematic reviews of TNF blockers for the treatment of AS, patients taking SIMPONI (golimumab), ENBREL (etanercept), REMICADE (infliximab), and HUMIRA (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (Machado et al, 2013). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (Maxwell et al, 2015). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, COSENTYX (secukinumab), and ACTEMRA (tocilizumab; not FDA approved for AS) (Chen et al, 2016). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating REMICADE (infliximab) for induction of remission, significantly more patients achieved remission at four weeks with infliximab compared to placebo (P<0.005)(Targan et al, 1997). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo (P=0.002 and P=0.02, respectively)(Present et al, 1999). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (Hyams et al, 2007).
- The safety and efficacy of ENTYVIO (vedolizumab) was demonstrated in two trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In one trial, a higher percentage of ENTYVIO-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, ENTYVIO did not achieve a statistically significant clinical response or clinical remission over placebo at week six (Sandborn et al, 2013; Sands et al, 2014).
- A meta-analysis evaluating CIMZIA (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; P=0.004) and remission (RR, 1.95; P<0.0001) over placebo. However, risk of infection was higher with certolizumab use (Shao et al, 2009).
- Additionally, HUMIRA (adalimumab), CIMZIA (certolizumab) and REMICADE (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; P<0.00001; RR, 1.74; P<0.0001 and RR, 1.66; P=0.0046, respectively) and maintain clinical remission (RR, 1.68; P=0.000072 with certolizumab and RR, 2.5; P=0.000019 with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (Behm et al, 2008). Other systematic reviews have further demonstrated the efficacy of these agents in CD (Singh et al, 2014).
- In a systematic review of patients with CD who had failed a trial with REMICADE (infliximab), the administration of HUMIRA (adalimumab) was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in zero to 19% of patients in up to four years of treatment (Ma et al, 2009).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or ENTYVIO (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (Chandar et al, 2015). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the two active treatments (P=0.95). No significant differences between natalizumab and vedolizumab were observed for rates of

serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab (P=0.007). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.

- The use of STELARA (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (Feagan et al, 2016). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (N=741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to one or more TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of <150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P=0.002 for 130 mg dose vs placebo; P=0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI <150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
    - UNITI-2 (N=628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P<0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
    - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SC every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (P=0.005 for every 8 week regimen vs placebo; P=0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated HUMIRA (adalimumab) for the treatment of HS (Kimball et al, 2016). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of two treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week zero, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
    - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (P=0.003) and 58.9% vs 27.6% in PIONEER II (P<0.001).
    - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
    - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (six to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with ORENCIA (abatacept) (P=0.0003). The time to flare was significantly different favoring abatacept (P=0.0002) (Ruperto et al, 2008).

- HUMIRA (adalimumab) was studied in a group of patients (four to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (Lovell et al, 2008).
- A double-blind, multicenter, randomized controlled trial compared HUMIRA (adalimumab) and placebo in 46 children ages six to 18 years with enthesitis-related arthritis (Burgos-Vargas et al, 2015). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, P=0.039). A total of seven patients (three placebo; four adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; P=0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, ENBREL (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; P=0.003) (Lovell et al, 2000). Ninety-four percent of patients who remained in an open-label four year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious AEs related to etanercept therapy after four years (Lovell et al, 2006).
- The approval of ACTEMRA (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; P<0.0001)(De Benedetti et al, 2012). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (Brunner et al, 2015). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; P<0.0024).
- In two trials in patients with SJIA, ILARIS (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (Ruperto et al, 2012).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; one each for KINERET (anakinra), ILARIS (canakinumab), and ACTEMRA (tocilizumab), and 2 for rilonacept (not FDA approved for JIA and not included in this review) (Tarp et al, 2016). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, HUMIRA (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (P<0.001) and placebo (P<0.001) groups, respectively (Saurat et al, 2008).
- More than 2,200 patients were enrolled in two published, pivotal, phase III trials that served as the primary basis for the FDA approval of STELARA (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter (Leonardi et al, 2008; Papp et al, 2008; Langley et al, 2015). In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (P<0.0001 for both). PASI 75 response was better maintained to at least one year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (P<0.0001)

(Leonardi et al, 2008). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo (P<0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every eight weeks. More partial responders at week 28 who received 90 mg every eight weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (Papp et al, 2008). A total of 70% (849 of 1,212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (Langley et al, 2015).

- In a study comparing ENBREL (etanercept) and STELARA (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (Griffiths et al, 2010).
- Approval of OTEZLA (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; P<0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; P<0.0001) at 16 weeks (Papp et al, 2015; Paul et al, 2015a).
    - Additional analyses of the ESTEEM trials have been published. In one (Thaçi et al, 2016), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al, 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- COSENTYX (secukinumab) was evaluated in two large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (N=738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
    - In FIXTURE (N=1,306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, ENBREL (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated COSENTYX (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (N=177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (Blauvelt et al, 2015).
    - In JUNCTURE (N=182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (Paul et al, 2015b).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of COSENTYX (secukinumab) (Blauvelt et al, 2015; Langley et al, 2014; Paul et al, 2015b).
- In the CLEAR study, COSENTYX (secukinumab) 300 mg SQ every four weeks and STELARA (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind,

randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; P<0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.

- A meta-analysis of seven Phase 3 clinical trials demonstrated the efficacy of COSENTYX (secukinumab) vs placebo and vs ENBREL (etanercept) in patients with PsO (Ryoo et al, 2016). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the one-year trials.
- The use of TALTZ (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (N=1,296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (Gordon et al, 2016; Taltz product dossier, 2016). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively (P<0.001 for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively (P<0.001 for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (N=1,224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (Griffiths et al, 2015). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (N=1,346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (Griffiths et al, 2015). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (Gordon et al, 2016). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The use of SILIQ (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (N=661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks zero, one, and two, followed by every two weeks to week 12 (Papp et al, 2016). This 12-week

induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥2 and those initially receiving placebo received brodalumab 210 mg every two weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (P<0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (N=1,831) and AMAGINE-3 (N=1,881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, STELARA (ustekinumab), and placebo (Lebwohl et al, 2015). Brodalumab was given at weeks zero, one, and two, followed by every two weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every two weeks or 140 mg every two, four, or eight weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every two weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.08 for brodalumab 140 mg vs ustekinumab).
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.007 for brodalumab 140 mg vs ustekinumab).
  - In both studies, the two brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every two weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- For most immunomodulators that are FDA approved for the treatment of PsO, the indication is limited to adults. In 2016, ENBREL (etanercept) received FDA approval for treatment of PsO in pediatric patients aged four years and older. Limited information from published trials is also available on the use of STELARA (ustekinumab) in adolescent patients (age 12 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (N=211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (Paller et al, 2008). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and

retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (P<0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including three infections) occurred in three patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (N=182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (Paller et al, 2016).

  - A 52-week, double-blind, placebo-controlled trial (N=110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (Landells et al, 2015). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (P<0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (Feldman, 2015). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with ENBREL (etanercept) plus MTX may be beneficial for therapy-resistant patients (Busard et al, 2014; Gottlieb et al, 2012).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, HUMIRA (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (P<0.00001) while ENBREL (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (P<0.00001 for both strengths vs placebo). The REMICADE (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group (P<0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (Schmitt et al, 2008).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (Nast et al, 2015a). A total of 25 randomized trials (N=11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for REMICADE (infliximab), 11.97 (95% CI, 8.83 to 16.23) for COSENTYX (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for STELARA (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for HUMIRA (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for ENBREL (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for OTEZLA (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.

Psoriatic arthritis (PsA)

- In two trials, PsA patients receiving HUMIRA (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 (P=0.012) in a trial (N=100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (P<0.001) (Genovese et al, 2007; Mease et al, 2005). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; P<0.001) (Mease et al, 2005).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of ENBREL (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo (P<0.0001). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 (P=0.0154) and 13% (P<0.0001) of placebo-treated patients (Mease et al, 2000). In a second trial, the mean annualized rate of change in the mTSS with ENBREL (etanercept) was -0.03 unit, compared to one unit with placebo (P<0.0001). At 24 weeks, 23% of etanercept

patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients (P=0.001). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; P<0.001) (Mease et al, 2004).

- The FDA approval of SIMPONI (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (N=405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (Kavanaugh et al, 2009).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year five were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every four weeks (Kavanaugh et al, 2014b).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [(≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (Kavanaugh et al, 2016).
- In another trial, more REMICADE (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (P<0.001) (Antoni et al, 2005).
- The efficacy of CIMZIA (certolizumab) in the treatment of PsA was established in one multicenter, double-blind, placebo controlled trial (N=409). Patients were randomized to receive placebo, CIMZIA 200 mg every two weeks, or CIMZIA 400 mg every four weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (Mease et al, 2014).
- The FDA-approval of STELARA (ustekinumab) for PsA was based on the results of two randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (N=615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; P<0.0001 for both comparisons); responses were maintained at week 52 (McInnes et al, 2013). Similar results were observed in the PSUMMIT 2 trial (N=312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (P<0.001) (Ritchlin et al, 2014).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (McInnes et al, 2013). At week 100 (Kavanaugh et al, 2015a), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on two multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 (Mease et al, 2015; McInnes et al, 2015). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; P<0.0001 vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.

  - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively (P<0.0001 for secukinumab 300 mg and 150 mg; P<0.05 for 75 mg vs placebo).
  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of OTEZLA (apremilast) was demonstrated in three placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the OTEZLA groups had ≥20% improvement in symptoms, as defined by ACR response criteria (Cutolo et al, 2013; Edwards et al, 2016; Kavanaugh et al, 2014a). Clinical improvements observed at 16 weeks were sustained at 52 weeks (Edwards et al, 2016; Kavanaugh et al, 2015b).
- A small, single-center randomized trial (N=100) compared REMICADE (infliximab), ENBREL (etanercept), and HUMIRA (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (Atteno et al, 2010). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of HUMIRA (adalimumab), ENBREL (etanercept), REMICADE (infliximab), and SIMPONI (golimumab) over 24 weeks for the treatment of PsA (Fénix et al, 2013). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of nine randomized controlled trials and six observational studies evaluated HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (Lemos et al, 2014). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (Ungprasert et al, 2016a). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: ENBREL [etanercept], REMICADE [infliximab], HUMIRA [adalimumab], and SIMPONI [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving CIMZIA (certolizumab), OTEZLA (apremilast), or STELARA (ustekinumab). Patients receiving COSENTYX (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (ORENCIA [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (Ungprasert et al, 2016b). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated REMICADE (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week eight was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all P<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (Rutgeerts et al, 2005). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (Hyams et al, 2012).
- In the ULTRA 2 study, significantly more patients taking HUMIRA (adalimumab) 160 mg at week zero, 80 mg at week two, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (Sandborn et al, 2012). These long term results confirm the findings of ULTRA 1. This eight-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical

remission (Reinisch et al, 2011). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for two of the secondary end points at week eight, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week eight. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of three randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (Zhang et al, 2016).

- SIMPONI (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks zero and two were compared to patients receiving placebo. At week six, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; P<0.0001 for both comparisons) (Sandborn et al, 2014b). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; P<0.001 and P=0.01, respectively) (Sandborn et al, 2014a).
- The safety and efficacy of ENTYVIO (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of ENTYVIO-treated patients achieved or maintained clinical response and remission over placebo at weeks six and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (Feagan et al, 2013). A systematic review and meta-analysis (N=606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (Bickston et al, 2014; Mosli et al, 2015).

Uveitis (UV)

- The safety and efficacy of HUMIRA (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in two randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (N=217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (Jaffe et al, 2016). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
    - VISUAL II (N=226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (Nguyen et al, 2016a). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; P=0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

CAPS, FMF, HIDS/MKD, and TRAPs

- The efficacy of KINERET (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n=11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (KINERET prescribing information, 2016). A cohort study of 26 patients followed for three to five years demonstrated sustained improvement in disease activity and inflammatory markers (Sibley et al, 2012).
- The efficacy and safety of ILARIS (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (ILARIS prescribing information, 2016).

Published data supports the use of canakinumab for these various CAPS phenotypes (Koné-Paut et al, 2011; Kuemmerle-Deschner et al, 2011; Lachmann et al, 2009).

- Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period. Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (ILARIS prescribing information, 2016).

Treatment Guidelines

- RA:
  - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib (Singh et al, 2016c).
  - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (Smolen et al, 2017).
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (ACR, 2016).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- JIA:
  - bwohl etican College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (Beukelman et al, 2011; Ringold et al, 2013).
    - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (Beukelman et al, 2011).
    - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is one of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (Ringold et al, 2013).
- UC:
  - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (Kornbluth et al, 2010). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.

- CD:
  - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. Maintenance therapy with TNF inhibitors is effective. An update to these guidelines is currently in process (Lichtenstein et al, 2009).
  - The American Gastroenterological Association (AGA) recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (Nguyen et al, 2017).
  - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (Sandborn, 2014).
  - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (Gomollón et al, 2017).
- Pregnancy in inflammatory bowel disease:
  - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (Nguyen et al, 2016b).
- PsO and PsA:
  - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (Hsu et al, 2012).
  - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011). Biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (>5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
  - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (Nast et al, 2015b). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least one synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
  - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (Gottleib et al, 2008; Menter et al, 2009b; Menter et al, 2011).
  - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate (Gossec et al, 2016; Ramiro et al, 2016).

- The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (Coates et al, 2016).

- AS:
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (van der Heijde et al, 2017).
  - The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (Ward et al, 2016).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (Levy-Clarke et al, 2014). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (Ozen et al, 2016).
  - No recent guidelines were identified for CAPS, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:
  - ACTEMRA (tocilizumab), COSENTYX (secukinumab), ENTYVIO (vedolizumab), ILARIS (canakinumab), INFLECTRA (infliximab-dyyb), KINERET (anakinra), OTEZLA (apremilast), REMICADE (infliximab), STELARA (ustekinumab), and TALTZ (ixekixumab) use in patients with hypersensitivity to any component of the product.
  - SILIQ is contraindicated in patients with Crohn's disease because SILIQ may cause worsening of disease.
  - ENBREL (etanercept) in patients with sepsis.
  - KINERET (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - REMICADE (infliximab) and INFLECTRA (infliximab-dyyb) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - ACTEMRA (tocilizumab), CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), REMICADE (infliximab), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ / XELJANZ XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.

  - In addition, CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), REMICADE (infliximab), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ (tofacitinib) all have warnings for increased risk of malignancies.
  - RITUXAN (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
  - SILIQ has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Increased lipid parameters and liver function tests with XELJANZ / XELJANZ XR (tofacitinib)
  - Increased incidence of CD and UC with COSENTYX (secukinumab) and TALTZ (ixekixumab); risk of new-onset CD or exacerbation of CD with SILIQ (brodalumab)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a five-year study in RA and a 10-year study in patients with early RA (Keystone et al, 2014a; Burmester et al, 2014b). In the five-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first six months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over five years in patients with RA (Keystone et al, 2014b). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 patient-years), and upper respiratory infections (rate of 7.3 per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.
    - Abatacept has been evaluated in two long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the seven year follow-up and a 52-week double-blind study (Westhovens et al, 2014). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 patient-years), malignancies (3.2 events per100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a five-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year one and year five, respectively.
    - Data from five RCTs of ACTEMRA (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least one dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (PY). The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (Genovese et al, 2013).
    - A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the ENBREL (etanercept) plus DMARD group and the DMARD alone group at six months, 12 months, and two years. At three years, withdrawals were significantly reduced in the

etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at six months, flu-like syndrome at six months and two years, infection at six months and two years, malignancy at 12 months and two years, pneumonia at 12 months, and serious infection at 12 months and two years between the etanercept plus DMARD group and the DMARD group (Lethaby et al, 2013).

- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (Strand et al, 2015b). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.

o PsO

- A total of 3,117 patients treated with at least one dose of STELARA (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least four years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with greater than or equal to five years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year five. The causes of death were considered related to cardiovascular events (n=5), malignancy (n=5), infection (n=3) and other causes (n=7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year one to year five, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (Papp et al, 2013).
- In a five-year extension study, a total of 2,510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (Kimball et al, 2015). Serious AEs were reported as a cumulative incidence of the entire five-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month six and remained stable through five years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (Kalb et al, 2015). Patients were followed for up to eight years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; P<0.001) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; P=0.002) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

o PsA

- Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (Kavanaugh et al, 2014b). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.

o Multiple indications

- One study looked at 23,458 patients who were treated with HUMIRA (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general

population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (Burmester et al, 2013b).
    - Pooled data from five Phase 3 trials of SQ golimumab over at least three years demonstrated a safety profile consistent with other TNF inhibitors (Kay et al, 2015). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
    - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (Capogrosso Sansone et al, 2015). All but one trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
    - Several recent meta-analyses evaluated the safety of TNF inhibitors.
        - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up one to 36 months) and seven open-label extension studies (follow-up six to 48 months) (Minozzi et al, 2016). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
        - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up two to 36 months) and six open-label extension trials (follow-up six to 48 months) (Bonovas et al, 2016). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
    - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
    - Do not give two immunomodulators together.
    - For XELJANZ / XELJANZ XR (tofacitinib), do not give with potent inhibitors of cytochrome P450 (CYP) 3A4; medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19; potent CYP3A4 inducers; and potent immunosuppressive drugs.
- Risk Evaluation and Mitigation Strategy (REMS)
    - STELARA (ustekinumab) has a REMS program in place, which consists of a communication plan regarding potential risk of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).
    - SILIQ (brodalumab) is available only through the SILIQ REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
        - Prescribers must be certified with the program.
        - Patients must sign a patient-prescriber agreement form.
        - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ACTEMRA (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe: 162 mg/0.9 mL	**RA:** 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose=800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response. >100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks.	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. Adjust dose for liver enzyme abnormalities, low platelet count and low ANC.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe.
CIMZIA (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsO:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as two 200 mg SQ injections in separate sites in the thigh or abdomen.
COSENTYX (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO	Each 300 mg dose is given as two subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		every 4 weeks	should be followed. If active PsA continues, consider 300 mg dose.	
ENBREL (etanercept)	Prefilled syringe: 25 mg and 50 mg Prefilled SureClick autoinjector: 50 mg Multiple-use vial: 25 mg	**RA, AS, PsA:** 50 mg SQ weekly **PsO (adults):** 50 mg SQ twice weekly for three months, then 50 mg weekly **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued **JIA:** NSAIDs glucocorticoids, or analgesics may be continued	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
ENTYVIO (vedolizumab)	Lyophilized cake for injection in single dose 20 mL vials: 300 mg	**CD and UC:** 300 mg administered by intravenous infusion at time zero, two and six weeks, and then every eight weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	ENTYVIO should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
HUMIRA (adalimumab)	Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL Single-use pen: 40 mg/0.8 mL Single-use vial: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX. **PJIA:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg SQ two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		dose of 80 mg SQ, followed by 40 mg SQ every other week starting one week after the initial dose. **CD in pediatric patients ≥6 years and older:** 17 kg to <40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg two weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg two weeks later (on day 150); maintenance dose is 40 mg every other week starting at week 4.		
ILARIS (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg)	Do not inject into scar tissue.
INFLECTRA (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Infuse over 2 hours. Do not administer with other drugs.
KINERET (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
ORENCIA (abatacept)	Vial: 250 mg Prefilled syringe: 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg.		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.
OTEZLA (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms.	May be taken with or without food. Do not crush, split, or chew the tablets.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily	Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	
REMICADE (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
RITUXAN (rituximab)	Vial: 100 mg 500 mg	**RA:** 1,000 mg IV every 2 weeks times two doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
SILIQ (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
SIMPONI/ SIMPONI ARIA (golimumab)	SmartJect® autoinjector: 50 mg and 100 mg Prefilled syringe: 50 mg and 100 mg ARIA, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **ARIA**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **ARIA**: give with MTX Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **ARIA**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
STELARA (ustekinumab)	Prefilled syringe: 45 mg and 90 mg Vial: 130 mg	**PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **CD**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight)	Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. STELARA for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least one hour. Rotate injection sites.
TALTZ (ixekizumab)	Prefilled syringe: 80 mg Autoinjector: 80 mg	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
XELJANZ / XELJANZ XR (tofacitinib)	Tablet: 5 mg Extended release Tablet: 11 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily	Patients may switch from XELJANZ 5 mg twice daily to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of XELJANZ in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended. Dose interruption is recommended for management of lymphopenia (< 500 cells/mm^3), neutropenia (absolute neutrophil count [ANC] < 500 cells/mm^3) and anemia. Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors.	May take with or without food. Swallow XELJANZ XR tablets whole; do not crush, split, or chew.

ANC=absolute neutrophil count; AS=ankylosing spondylitis; DMARD=disease-modifying anti-rheumatic drug; HS=hidradenitis suppurativa; IV=intravenous infusion; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID= neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO= plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ACTEMRA (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA and PJIA.	No dose adjustment in mild impairment. Not studied in moderate to severe impair-ment.	Not studied in patients with impairment.	Uncategorized† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
CIMZIA (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Safety and effectiveness have not been established.	No data	No data	Uncategorized† Limited data from ongoing pregnancy registry not sufficient to inform risks. Unknown whether excreted in breast milk, but data suggest systemic exposure to a breastfed infant is expected to be low; risks and benefits should be considered.
COSENTYX (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
ENTYVIO (vedolizumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
ENBREL (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Pregnancy category B* Present in low levels in breast milk; use caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
HUMIRA (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA (ages 2 years and older) and CD (6 years and older).	No data	No data	Uncategorized† Present in low levels in breast milk; use caution.
ILARIS (canakinumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Uncategorized † Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; use caution.
INFLECTRA (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
KINERET (anakinra)	Use caution.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day	No data	Pregnancy category B* Unknown whether excreted in breast milk; use caution.
ORENCIA (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <6 years. SQ formulation has not been studied in patients <18 years.	No data	No data	Uncategorized † Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
OTEZLA (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30 mL/min).	No dosage adjustment necessary.	Pregnancy category C* Unknown whether excreted in breast milk; use caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
REMICADE (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recommended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
RITUXAN (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and effectiveness have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
SILIQ (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response.	Safety and effectiveness in <18 years have not been established.	No data	No data	Uncategorized † There are no human data in pregnant women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
SIMPONI/ SIMPONI ARIA (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV ARIA: Use caution.	Safety and effectiveness in <18 years have not been established.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
STELARA (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have not been established.	No data	No data	Uncategorized † Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
TALTZ (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Uncategorized † There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
XELJANZ / XELJANZ XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Reduce dose to 5 mg daily in moderate to severe impairment.	Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment.	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

CrCl=creatinine clearance; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at six months, but abatacept demonstrated greater efficacy after one year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (Schiff et al, 2008).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over two years in a single-blind study (Schiff et al, 2014).
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (Gabay et al, 2013). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (Porter et al, 2016).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (Gottenberg et al, 2016). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population (Manders et al, 2015).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The proportion of

patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001).
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (Griffiths et al, 2010).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (Langley et al, 2014).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (Lebwohl et al, 2015).
    - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (Park et al, 2013; Park et al, 2016; Park et al, 2017; Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017).
    - More comparative studies are needed.
- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (Singh et al, 2016c; Smolen et al, 2017). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- For the management of PsO, biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011; Nast et al, 2015b). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX (Gossec et al, 2016; Ramiro et al, 2016). For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (Coates et al, 2016).
- In patients with JIA and involvement of ≥5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (Beukelman et al, 2011). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (Ringold et al, 2013).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (Kornbluth et al, 2010). Other immunomodulators were not indicated for UC when these guidelines were written.
- Based on ACG guidelines, the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (Lichtenstein et al, 2009). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (Gomollón et al, 2017).
- Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy (Nguyen et al, 2016b).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (van der Heijde et al, 2017). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly

recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (Ward et al, 2016).

- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (Levy-Clarke et al, 2016).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

REFERENCES

- ACTEMRA prescribing information. Genentech, Inc. South San Francisco, CA. September 2016.
- American College of Rheumatology. Position statement on biosimilars. April 2016. http://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf. Accessed March 14, 2017.
- Antoni C, Krueger GG, de Vam K, et al. IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005;64(8):1150-7.
- ARCALYST prescribing information. Regeneron Pharmaceuticals, Inc. Tarrytown, NY. September 2016.
- Atsumi T, Yamamoto K, Takeuchi T, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016;75:75-83.
- Atteno M, Peluso R, Costa L, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol. 2010;29:399-403.
- Baeten D, Sieper J, Braun J, et al for the MEASURE 1 Study Group and MEASURE 2 Study Group. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med. 2015; 373(26):2534-48.
- Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews. 2008, Issue 1. Art. No.: CD006893. doi: 10.1002/14651858. CD006893.
- Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011;63(4):465-482.
- Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis (review). Cochrane Database Syst Rev. 2014;8:CD007571. doi: 10.1002/14651858.
- Bijlsma JW, Welsing PM, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet. 2016;388:343-55.
- Bingham CO, Mendelsohn AM, Kim L, et al. Maintenance of clinical and radiographic benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: week-112 efficacy and safety results of the open-label long-term extension of a phase III, double-blind, randomized, placebo-controlled trial. Arthritis Care Res. 2015;67:1627-1636.
- Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484-93.
- Bonovas S, Minozzi S, Lytras T, et al. Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):35-54.
- Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. Lancet. 2002;359(9313):1187-93.
- Braun J, van der Horst-Bruinsma IE, Huang F, et al. Clinical efficacy and safety of etanercept vs sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum. 2011;63(6):1543-51.
- Brunner H, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomized, double-blind withdrawal trial. Ann Rheum Dis. 2015;74:1110-117. doi:10.1136/annrheumdis-2014-205351.
- Burmester GR, Blanco R, Charles-Schoeman C, et al for the ORAL Step Investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomized phase 3 trial. Lancet. 2013[a];381:451-60.
- Burmester GR, Matucci-Cerinic M, Mariette X, et al. Safety and effectiveness of adalimumab in patients with rheumatoid arthritis over 5 years of therapy in a phase 3b and subsequent postmarketing observational study. Arthritis Res Ther. 2014b;16(1):R24. doi: 10.1186/ar4452.
- Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013[b];72: 517–24.
- Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab vs intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis. 2014a;73:69-74.
- Burmester GR, Rubbert-Roth A, Cantagrel A, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). Ann Rheum Dis. 2016;75:68-74.
- Busard C, Zweegers J, Limpens J, et al. Combined use of systemic agents for psoriasis: a systematic review. JAMA Dermatol. 2014;150(11):1213-1220.
- Calin A, Dijkmans BAC, Emery P, et al. Outcomes of a multicentre randomized clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004; 63:1594-600.

- Capogrosso Sansone A, Mantarro S, Tuccori M, et al. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Drug Saf. 2015;38:869-888.
- Chandar AK, Singh S, Murad MH, et al. Efficacy and safety of natalizumab and vedolizumab for the management of Crohn's Disease: A systematic review and meta-analysis. Inflamm Bowel Dis. 2015;21:1695-1708.
- Chen C, Zhang X, Xiao L, et al. Comparative effectiveness of biologic therapy regimens for ankylosing spondylitis: a systematic review and a network meta-analysis. Medicine (Baltimore). 2016;95(11):e3060. doi: 10.1097/MD.0000000000003060.
- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907-16.
- CIMZIA prescribing information. UCB, Inc. Smyrna, GA. January 2017.
- Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016;68(5):1060-71.
- Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54: 2793-806.
- Combe B, Dasgupta B, Louw I, et al. Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. Ann Rheum Dis. 2014;73:1477-1486.
- COSENTYX prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. January 2016.
- Cutolo M, Myerson GE, Fleischmann RM, et al. Long-term (52-week) results of a Phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis (PALACE 2). Abstract session presented at: The American College of Rheumatology and Association of Rheumatology Health Professionals Annual Meeting; 2013 October 25-30; San Diego, CA.
- Davis JC, van der Heijde DM, Braun J, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. Ann Rheum Dis. 2008;67:346-52.
- De Benedetti, Brunner H, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385-95.
- Deodhar A, Braun J, Inman RD, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. Ann Rheum Dis. 2015;74:757-61.
- Donahue KE, Jonas DE, Hansen RA, et al. Drug therapy for rheumatoid arthritis in adults: an update [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Apr. (Comparative Effectiveness Reviews, No. 55.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK97388/. Accessed March 17, 2017.
- Drugs@FDA. Food and Drug Administration. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 17, 2017.
- Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomized, controlled trial (PALACE 3). Ann Rheum Dis. 2016;75(6):1065-73.
- Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009;60(8):2272-83.
- Emery P, Keystone E, Tony H, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biological: results from a 24-week multicenter randomized placebo-controlled trial. Ann Rheum Dis. 2008;67:1516-23.
- ENBREL prescribing information. Amgen. Thousand Oaks, CA. November 2016.
- ENTYVIO prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. May 2014.
- Feagan BG, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.
- Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375:1946-60.
- Fénix-Caballero S, Alegre-del Rey EJ, Castano-Lara R, et al. Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. J Clin Pharm Ther. 2013;38(4):286-93.
- Fleischmann RM, Halland AM, Brzosko M, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol. 2013;40(2):113-26.
- Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6): 495-507.
- Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every four weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009; 68:805-11.
- Furst DE, Kavanaugh A, Florentinus S, et al. Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy. Rheumatology. 2015;54:2188-2197.
- Gabay C, Emery P, van Vollenhoven R, et al. ADACTA Study Investigators. Tocilizumab monotherapy vs adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013; 381(9877):1541-50.
- Galvao TF, Zimmermann IR, da Mota LM, et al. Withdrawal of biologic agents in rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2016;35(7):1659-68.
- Genovese M, McKay J, Nasonov E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2008;58(10):2968-80.
- Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept vs intravenous abatacept: A phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011;63(10):2854-64.
- Genovese MC, Mease PJ, Thomson GTD, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheum. 2007;34:1040-50.
- Genovese MC, Rubbert-Roth A, Smolen JS, et al. Long-term safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol. 2013;40: 768–80. doi:10.3899/jrheum.120687.
- Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. J Crohns Colitis. 2017;11(1):3-25.
- Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375:345-56.

- Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. N Engl J Med. 2002;346(18):1349-56.
- Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis. 2016;75(3):499-510.
- Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795-810.
- Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. JAMA. 2016;316(11):1172-1180.
- Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2012;167:649-657.
- Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386:541-51.
- Griffiths CE, Strober BE, van de Kerkhof P, et al; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28.
- Gulliver W, Zouboulis CC, Prens E, et al. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016;17(3):343-51.
- Haraoui B, Bokarewa M, Kallmeyer I, et al. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior tumor necrosis factor inhibitor: the RESET trial. J Rheumatol. 2011;38; 2548-56.
- Hazlewood GS, Barnabe C, Tomlinson G, et al. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: a network meta-analysis. Cochrane Database of Systematic Reviews. 2016, Issue 8. Art. No.: CD010227. doi: 10.1002/14651858.CD010227.pub2.
- Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148(1):95-102.
- HUMIRA prescribing information. AbbVie Inc. North Chicago, IL. June 2016.
- Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132(3):863-73; quiz 1165-6.
- Hyams JS, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10(4):391-399.
- ILARIS prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. December 2016.
- INFLECTRA prescribing information. Hospira. Lake Forest, IL. April 2016.
- Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med. 2016;375:932-43.
- Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy vs methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis. 2010;69(1):88-96.
- Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;151(9):961-9.
- Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-86.
- Kavanaugh A, McInnes IB, Mease P, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomized, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis. 2014[b];73(9):1689-94. doi: 10.1136/annrheumdis-2013-204902
- Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Long-term (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol. 2015[b];42:479-88.
- Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3, randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014[a];73(6):1020-6. doi: 10.1136/annrheumdis-2013-205056.
- Kavanaugh A, Puig L, Gottlieb AB, et al; PSUMMIT 1 Study Group. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, placebo-controlled phase III trial. Arthritis Care Res. 2015[a];67(12):1739-1749.
- Kavanaugh A, van der Heijde D, Beutler A, et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 years of a randomized, placebo-controlled study. Arthritis Care Res (Hoboken). 2016;68(2):267-74.
- Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomized, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis. 2015;74(3):538-46. doi: 10.1136/annrheumdis-2013-204195.
- Keystone E, Landewe R, van Vollenhoven R, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. Ann Rheum Dis. 2014[a];73(12):2094-100. doi: 10.1136/annrheumdis-2013-203695.
- Keystone E, van der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. Arthritis Rheum. 2008;58(11):3319-29.
- Keystone EC, Breedveld FC, van der Heijde D, et al. Long-term effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. J Rheumatol. 2014[b];41(1):5-14. doi: 10.3899/jrheum.130543.
- Keystone EC, Genovese MC, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension. J Rheumatol. 2013[a];40; 1097-1103.
- Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumor necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68(6):789-96.
- Keystone ED, van der Heijde D, Kavanaugh A, et al. Clinical, functional, and radiographic benefits of long-term adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. J Rheum. 2013[b];40(9): 2-11.
- Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med. 2016;375:422-34.
- Kimball AB, Rothman KJ, Kricorian G, et al. OBSERVE-5: Observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results. J Am Acad Dermatol. 2015;72(1):115-22. doi: 10.1016/j.jaad.2014.08.050

- KINERET prescribing information. Swedish Orphan Biovitrum (SOBI, INC). Stockholm, Sweden. May 2016.
- Kivitz A, Olech E, Borofsky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res. 2014;66:1653-61.
- Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther. 2011;13(1):R34.
- Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501-23.
- Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti–tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis. Forty-eight–week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010;62(4): 917–28.
- Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63:609-21.
- Kuemmerle-Deschner JB, Hachulla E, Cartwright R, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis. 2011;70:2095-2102.
- Lachmann HJ, Koné-Paut I, Keummerle-Deschner JB, et al. Use of Canakinumab in the Cryopyrin Associated Periodic Syndrome. N Engl J Med. 2009;360:2416-25.
- Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. J Am Acad Dermatol. 2015;73:594-603.
- Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24 week results of a double-blind randomized placebo-controlled Phase 3 study. Ann Rheum Dis. 2014;73:39-47.
- Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis – results of two phase 3 trials. N Engl J Med. 2014;371:326-38.
- Langley RG, Lebwohl M, Krueger GG, et al for the Phoenix 2 Investigators. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate to severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol. 2015;172(5):1371-1383.
- Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373:1318-28.
- Lee EB, Fleischmann R, Hall S, et al for the Oral Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370:2377-86.
- Lemos LLP, de Oliveira Costa J, Almeida AM, et al. Treatment of psoriatic arthritis with anti‐TNF agents: a systematic review and meta‐analysis of efficacy, effectiveness and safety. Rheumatol Int. 2014;34:3145-1360.
- Leonardi C, Kimball A, Papp K, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665-74.
- Lethaby A, Lopez-Olivo MA, Maxwell L, et al. Etanercept for the treatment of rheumatoid arthritis (Review). The Cochrane Collaboration. Cochrane Library. 2013;5:1-452.
- Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121(3):785-96.
- Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465-83.
- Lopez-Olivio MA, Amezaga Urruela M, McGahan L, et al. Rituximab for rheumatoid arthritis. Cochrane Database Syst Reviews. 2015, Issue 1. Art. No.: CD007356. doi: 10.1002/14651858.CD007356.pub2.
- Lovell D, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008; 359(8):810-20.
- Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med. 2000;342:763-9.
- Lovell DJ, Reiff A, Jones OY, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2006;54:1987-94.
- Ma C, Panaccione R, Heitman SJ, et al. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. Aliment Pharmacol Ther. 2009;30:977-86.
- Machado MA, Barbaos MM, Almeida AM, et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int. 2013;33(9):2199-2213. doi: 10.1007/s00296-013-2772-6.
- Manders SH, Kievit W, Adang E, et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Research & Therapy. 2015;17:134.
- Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. Cochrane Database Syst Rev. 2009;(4):CD007277.
- Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev. 2015, Issue 4. Art. No.: CD005468. doi: 10.1002/14651858.CD005468.pub2.
- McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780-9.
- McInnes IB, Mease PJ, Kirkham B, et al for the FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(9999):1137-46.
- Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73:48-55.
- Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis. Arthritis Rheum. 2005; 52(10):3279-89.
- Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet. 2000;356;385-90.
- Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy and effect on disease progression. Arthritis Rheum. 2004;50:2264-72.
- Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373(14):1329-39.

- Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58:826-50.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5: Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62:114-35.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009[a];60:643-59.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009[b]; 61(3):451-85.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;(1):137-74.
- Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005121. doi: 10.1002/14651858. CD005121.pub3.
- Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.
- Mosli MH, MacDonald JK, Bickston SJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systemic review and meta-analysis. Inflamm Bowel Dis. 2015;21:1151-9.
- Nast A, Gisondi P, Ormerod AD, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris-update 2015-short version-EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015[b];29(12):2277-94.
- Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: a systematic review and meta-analysis. J Invest Dermatol. 2015[a];135(11):2641-8.
- Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005, Issue 3. Art. No.: CD005113. doi: 10.1002/14651858.CD005113.pub2.
- Nguyen GC, Loftus EV, Hirano I, et al. American Gastroenterological Institute guideline on the management of Crohn's disease after surgical resection. Gatroenterology. 2017;152(1):271-5.
- Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology. 2016[b];150:734-57.
- Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet. 2016[a];388:1183-92.
- Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumor necrosis factor α and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology. 2007;46:1140-7.
- O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369 (4):307-18.
- ORENCIA prescribing information. Bristol Myers Squibb. Princeton, NJ. June 2016.
- OTEZLA prescribing information. Celgene Corporation. Summit, NJ. December 2015.
- Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis. 2016;75:644-51.
- Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358:241-51.
- Paller AS, Siegfried EC, Pariser DM, et al. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. J Am Acad Dermatol. 2016;74:280-7.
- Papp K, Langley R, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675-84.
- Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE 4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.
- Papp KA, Griffiths CEM, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Derm. 2013;168: 844–54.
- Papp KA, Reich K, Paul C, et al. A prospective, phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175:273-86.
- Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605-1612.
- Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther. 2016;18:25. doi: 10.1186/s13075-016-0930-4.
- Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76(2):346-54.
- Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis over 52 weeks: a phase III randomized, controlled trial (ESTEEM 2). Br J Dermatol. 2015[a];173:1355-56.
- Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015[b];29(6):1082-90. doi: 10.1111/jdv.12751.
- Porter D, van Melckebeke J, Dale J, et al. Tumor necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet. 2016;388:239-47.
- Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999 May 6;340(18):1398-405.
- Ramiro S, Smolen JS, Landewe R, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2016;75(3):490-8.
- Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60: 780–7.
- REMICADE prescribing information. Janssen Biotech. Horsham, PA. October 2015.

- Rich P, Gooderham M, Bachelez H, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). J Am Acad Dermatol. 2016;74(1):134-42.
- Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis. Arthritis & Rheumatism. 2013;65(10):2499-2512.
- Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990-999.
- RITUXAN prescribing information. Genentech, Inc. South San Francisco, CA. August 2014.
- Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367: 2396-406. doi: 10.1056/NEJMoa1205099.
- Ruperto N, Lovell DJ, Quartier P, et al; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383-91.
- Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.
- Ryoo JY, Yang HJ, Ji E, Yoo BK. Meta-analysis of the efficacy and safety of secukinumab for the treatment of plaque psoriasis. Ann Pharmacother. 2016;50(5):341-51.
- Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology. 2014;147:702-5.
- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate to severe ulcerative colitis. Gastroenterology. 2014a;146(1):96-109. doi: 10.1053/j.gastro.2013.05.048.
- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014b;146:96-109.
- Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-721.
- Sandborn WJ, Van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142: 257–65.
- Sands BE, Feagan BG, Rutgeerts P, et al. Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed. Gastr. 2014;147:618-627.
- Saurat JH, Stingl G, Dubertret L, et al; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.
- Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67:1096-1103.
- Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept vs adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014;73:86-94.
- Schmitt J, Zhang Z, Wozel, G, et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Derm. 2008;159:513-26.
- Shao L-M, Chen M-Y, Chen Q-Y, et al. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009;29(6):605-14.
- Sibley CH, Plass N, Snow J, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra. A cohort study to determine three- and five-year outcomes. Arthritis Rheum. 2012;64(7): 2375-86.
- Sieper J, Kivitz A, van Tubergen A, et al. Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. Arthritis Care Res. 2015[a];67(10):1475-1480.
- Sieper J, Landewe R, Rudwaleit M, et al. Effects of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis. Arthritis & Rheumatology. 2015[b];67(3):668-677.
- SILIQ prescribing information. Valeant Pharmaceuticals. Bridgewater, NJ. February 2017.
- SIMPONI ARIA prescribing information. Janssen Biotech, Inc. Horsham, PA. January 2017.
- SIMPONI prescribing information. Janssen Biotech, Inc. Horsham, PA. January 2017.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug failure: a Cochrane systematic review and network meta-analysis. Cochrane Database of Systematic Reviews. 2016[b], Issue 11. Art. No.: CD012437. doi: 10.1002/14651858.CD012437.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics; a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews. 2017, Issue 3. Art. No.: CD012591. doi: 10.1002/14651858.CD012591.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews. 2016[a], Issue 5. Art. No.: CD012183. doi: 10.1002/14651858.CD012183.
- Singh JA, Saag KG, Bridges L Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016[c];68(1):1-26.
- Singh S, Kumar S, Pardi D, et al. Comparative efficacy of biologic therapy in biologic naïve patients with Crohn's disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014;89:1621-35.
- Smolen J, Landewe R, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomized controlled trial. Ann Rheum Dis. 2009[a];68:797-804.
- Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet. 2008;371(9617):987-97.
- Smolen JS, Emery P, Ferraccioli GF, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomized, placebo-controlled trial. Ann Rheum Dis. 2015[a];74:843-850. doi:10.1136/annrheumdis-2013-204632

- Smolen JS, Kay J, Doyle M, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor inhibitors: findings with up to five years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study. Arthritis Res Ther. 2015[b];17(1):14. doi: 10.1186/s13075-015-0516-6.
- Smolen JS, Kay J, Doyle MK, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomized, double-blind, placebo-controlled, phase III trial. Lancet. 2009[b];374(9685):210-21.
- Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Mar 6 [Epub]. doi: 10.1136/annrheumdis-2016-210715.
- STELARA prescribing information. Janssen Biotech. Horsham, PA. September 2016.
- Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015[b];17:362. doi 10.1186/s13075-015-0880-2.
- Strand V, Burmester GR, Zerbini CAF, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. Arthritis Care Res. 2015[a];67(4):475-483.
- TALTZ AMCP dossier. Eli Lilly and Company, Indianapolis, IN. March 2016.
- TALTZ prescribing information. Eli Lilly and Company, Indianapolis, IN. March 2016.
- Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997;337(15):1029-35.
- Tarp S, Amarilyo G, Foeldvari I, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatology. 2016;55:669-79.
- Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti–TNF-a biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145(6):1459-1463.
- Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400-9.
- Thaçi D, Kimball A, Foley P, et al. Apremilast, an oral phosphodiesterase inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials. J Eur Acad Dermatol Venereol. 2017;31(3):498-506.
- TYSABRI prescribing information. Biogen Idec Inc., Cambridge, MA. May 2016.
- Ungprasert P, Thongprayoon C, Davis JM. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis. Semin Arthritis Rheum. 2016[a];45(4):428-38.
- Ungprasert P, Thongprayoon C, Davis JM. Indirect comparisons of the efficacy of subsequent biological agents in patients with psoriatic arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta analysis. Clin Rheumatol. 2016;35:1795-1803.
- van der Heijde D, Dijkmans B, Geusens P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52(2):582-91.
- van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Arthritis Rheum. 2006;54(7):2136-46.
- van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017 Jan 13 [Epub]. doi: 10.1136/annrheumdis-2016-210770.
- van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving MTX. Twelve-month data from a twenty-four–month Phase III randomized radiographic study. Arthritis Rheum. 2013;65(3): 559-70.
- Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis & Rheumatology. 2016;68(2):282-98. doi 10.1002/ART.39298.
- Weinblatt ME, Bingham CO, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013;72: 381-89.
- Westhovens R, Kremer JM, Emery P, et al. Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. Clin Exp Rheumatol. 2014;32(4):553-62.
- Wiens A, Correr CJ, Venson R, et al. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73.
- XELJANZ / XELJANZ XR prescribing information. Pfizer, Inc. New York, NY. February 2016.
- Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72:1613-1620.
- Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76(2):355-63.
- Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 2016;18:82. doi: 10.1186/s13075-016-0981-6.
- Zhang ZM, Li W, Jiang XL. Efficacy and safety of adalimumab in moderately to severely active cases of ulcerative colitis: a meta-analysis of published placebo-controlled trials. Gut Liver. 2016;10(2):262-74.
- Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurative/acne inversa. J Eur Acad Dermatol Venereol. 2015;29(4):619-44.

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Therapeutic Class Overview
Multiple Sclerosis Agents

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is the leading cause of disability in young and middle-aged people in developed areas of the world *(MS Coalition 2017)*. MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons *(Goodin et al 2002)*. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for 80 to 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Progressive relapsing MS (PRMS) patients have a continuous decline in function while experiencing occasional attacks. Only 5% of MS patients have PRMS *(Goodin et al 2002, Sanvito et al 2011, National MS Society 2014a)*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 2.3 million people worldwide have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men *(National MS Society 2014b)*.
- Diagnosis of MS requires evidence of damage in a least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion *(Polman et al 2011)*. Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions *(Lublin et al 2014)*.
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) *(Miller et al 2012)*. Evaluation includes an extensive patient history, neurological examination, laboratory tests to rule out other possible causes, MRI to evaluate for new disease and signs of more chronic damage, and lumbar puncture.
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses and delay disease and disability progression *(Goodin et al 2002)*. The 2002 American Academy of Neurology and the 2008 National MS Society guidelines recommend the use of interferon beta (IFNβ) products or glatiramer acetate as first-line therapy in all patients with clinically definite RRMS and in select patients with CIS *(Goodin et al 2002, Miller et al 2008)*. The MS Coalition, the American Academy of Neurology, and the Association of British Neurologists guidelines support access to the available DMTs for patients with MS. There are currently no recent universal algorithms to determine the order of product selection. It is suggested that the most appropriate agent may be selected on an individual basis and monitored for clinical response and tolerability *(Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, Scolding et al 2015)*.
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) [listed as a potassium channel blocker].

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	-
Aubagio (teriflunomide)	-
Avonex (interferon β-1a)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-
Lemtrada (alemtuzumab)	-
mitoxantrone*	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-
Zinbryta (daclizumab)	-

†Glatopa by Sandoz is the FDA-approved generic for the Copaxone (glatiramer acetate) 20 mg once daily dosage form.
*Although brand Novantrone has been discontinued, generic mitoxantrone remains available.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)‡	✔	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-
Avonex (IM interferon β-1a)	-	✔	✔	✔	✔	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	✔	✔	-
Copaxone/Glatopa (glatiramer acetate)	-	✔	-	-	-	-
Gilenya (fingolimod)	-	✔	✔	✔	-	-
Lemtrada (alemtuzumab)	-	✔ (3rd line)*	-	-	-	-
mitoxantrone	-	✔ (2nd line)	✔ (neurologic disability)	✔	-	✔ §
Ocrevus (ocrelizumab)	-	✔	-	-	-	✔ ¶
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-
Rebif (interferon β-1a)	-	✔	✔	✔	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-
Tysabri (natalizumab)	-	✔ †	-	-	-	-
Zinbryta (daclizumab)	-	✔ (3rd line)*	-	-	-	-

IM=intramuscular; SC=subcutaneous
‡Ampyra is indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.
*Because of their safety profile, Lemtrada and Zinbryta should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS
†Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.
§Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications.
¶Ocrevus is approved for PPMS.

(Prescribing information: Ampyra 2016, Aubagio 2016, Avonex 2016, Betaseron 2016, Copaxone 2016, Extavia 2016, Gilenya 2016, Glatopa 2016, Lemtrada 2016, mitoxantrone 2017, Novantrone 2012, Ocrevus 2017, Plegridy 2016, Rebif 2015, Tecfidera 2017, Tysabri 2016, Zinbryta 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses and delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on magnetic resonance imaging (MRI), and disability progression for the interferons and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al, 1995, The IFNβ Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a subcutaneous [SC]), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. The results of several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to higher dose Rebif (IFNβ-1a SC 3 times weekly or every other day) or glatiramer acetate *(Khan et al 2001a, Khan et al 2001b, Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing interferons with glatiramer acetate, there were no significant differences between interferons and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given interferons than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; P=0.002).
  - While MRI outcomes analysis showed that effects on newer enlargingT2- or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given interferons than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; P=0.004, and MD −0.20, 95% CI: −0.33 to −0.07; P=0.003, respectively).
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and secondary progressive MS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N=368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly

for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; P=0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (P<0.001). In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of interferon NAb *(Govindappa et al 2015)*. NAb development was most frequent with interferon β-1b, followed by interferon β-1a SC, and lowest with interferon β-1a IM. Higher doses were associated with a higher rate of NAb development.

- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The annualized relapse rate (ARR) for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (P=0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (P=0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (P=0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another first-line therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing inadequate response to IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared. A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs. ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27. *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon ß-1a) in adult patients with MS (N=1516) were evaluated in ADVANCE, a Phase 3, multi-center, randomized, placebo-controlled trial. Eligible adult patients had RRMS with baseline Expanded Disability Status Scale (EDSS) score ≤5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon ß-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon ß-1a every 2 week group (ARR=0.256; P=0.0007) and peginterferon ß-1a every 4 week group (ARR=0.288; P=0.0114) compared to placebo (ARR=0.397).
  - There were also significant differences between the peginterferon ß-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (P=0.0003 and P=0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period was significantly lower in the peginterferon ß-1a groups (both 6.8%; P=0.0383 for every 2 weeks group; P=0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon ß-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; P<0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon ß-1a every 2 weeks compared to placebo (P<0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon ß-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon ß-1a were identified in <1% of all groups after 1 year (peginterferon ß-1a every 2 weeks, 4 patients; peginterferon ß-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAbdevelopment to peginterferon ß-1a over 2 years showed <1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon ß-1a (the “placebo-switch group”). Peginterferon ß-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower

in the peginterferon ß-1a every 2 weeks group (ARR 0.221; P=0.0001 vs placebo-switch group; P=0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon ß-1a every 4 week group (ARR 0.291). The peginterferon ß-1a every 4 week group (ARR 0.291; P=NS vs placebo-switch group) was not significantly different than the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon ß-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weight hyperintense MRI lesions over 2 years was numerically lower with the peginterferon ß-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2014)*.

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; P<0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly (P<0.001 for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a. Patients switched from IFNβ-1a to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; P values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; P values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24 month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both P<0.0001) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (O'Connor et al, 2011) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
- The percentage of patients with confirmed disability progression was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; P=0.03) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in patients with RRMS. There were 1237 patients enrolled, and the trial duration was 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl

fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.

- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab and IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two randomized, Phase 3, open-label trials in patients with relapsing forms of MS – CARE-MS 1 and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g intravenously for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS 1 trial enrolled treatment-naïve patients with MS (N=581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (N=840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on interferon beta or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS 1 trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC (P<0.0001). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%).
  - In the CARE-MS II trial, alemtuzumab significantly reduced relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab (P<0.0001). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab (P=0.0084).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS 1 and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year *(Garnock-Jones 2014)*.

Zinbryta (daclizumab)

- The efficacy and safety of daclizumab were studied in 2 pivotal trials: SELECT and DECIDE. The primary outcome measure in both studies was the ARR.
  - SELECT was a 52-week, Phase 2, double-blind, placebo-controlled, multicenter, RCT (N=621) that compared low and high doses of daclizumab to placebo *(Gold et al 2013)*. The 52-week extension study (entitled SELECTION)

assessed the safety and immunogenicity of extended treatment with daclizumab *(Giovannoni et al 2014)*. The SELECTED study enrolled 90% of patients who completed SELECTION and assessed the long-term safety and efficacy of daclizumab *(Gold et al 2016)*. At 52 weeks, daclizumab demonstrated a statistically significant effect on the ARR compared to placebo (0.211 vs 0.458; 54% relative reduction in ARR, P<0.0001) *(Gold et al 2013)*. Reductions in MS disease activity achieved during the first year of monotherapy with daclizumab were sustained, while the risk of adverse events and immunogenicity did not appear to increase during the second year of treatment *(Giovannoni et al 2014)*. The adverse event incidence did not increase with extension of therapy into a third year in SELECTED; the safety profile was similar to that previously observed.

- DECIDE was a 144-week, Phase 3, double-blind, active-control, multicenter, RCT (N=1841) that compared daclizumab 150 mg monthly to Avonex (IFNβ-1a) 30 mcg weekly *(Kappos et al 2015)*. Daclizumab had a statistically significant effect on the ARR compared to Avonex (0.216 vs 0.393; 45% relative reduction in ARR, P<0.0001).

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017[a], Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multi-center, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFN beta-1a; 44 mcg administered by SC injection 3 times per week) in 1656 patients with RMS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
    - Ocrelizumab achieved statistically significant reductions in the ARR vs. Rebif across both trials (primary endpoint).
      - OPERA I (0.16 vs. 0.29; 46% lower rate with ocrelizumab; P<0.001)
      - OPERA II (0.16 vs. 0.29; 47% lower rate; P<0.001)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs. Rebif (9.1% vs. 13.6%; hazard ratio [HR]=0.60, 95% CI: 0.45 to 0.81; P<0.001). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs. 10.5%; HR=0.60, 95% CI: 0.43 to 0.84; P=0.003. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs. 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; P=0.02).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs. Rebif (secondary endpoint).
      - OPERA I: 0.02 vs. 0.29 (rate ratio=0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; P<0.001)
      - OPERA II: 0.02 vs. 0.42 (rate ratio=0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; P<0.001)
    - The most common adverse events (AEs) were infusion-related reactions and infections.
  - No opportunistic infections, including PML were reported in any group over the duration of either trial.
    - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs. 0.2% (2/826) of Rebif-treated patients.
    - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
      - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
  - ORATORIO was an event-driven, Phase 3, double-blind, multi-center, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks

apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. DB treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.

- The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs. 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline (BL), with nearly 50% fewer lesions in the placebo group (1.21 vs. 0.6) (*FDA Medical and Summary Reviews 2017*).
- The percentages of patients with 12-week confirmed disability progression (CDP; primary endpoint) were 32.9% with ocrelizumab vs. 39.3% with placebo (HR=0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; P=0.03).
- The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs. 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; P=0.04).
- Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
  - The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
  - From BL to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (P<0.001).
  - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs. 1.09% with placebo (P=0.02).
- Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs. placebo.
- Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs. 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
  - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the OL extension phase in which all patients received ocrelizumab.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the walking speed by about 25% in approximately one-third of MS patients as measured by the timed 25-foot walk (T25FW) *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFN β-1a IM) and Betaseron (IFN β-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.

- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a clinically definite MS diagnosis by 45% compared to placebo in patients with CIS (P=0.005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; P=0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of clinically definite MS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; P=0.0005). Over the 2 year extension, the baseline-adjusted proportions of patients who developed clinically definite MS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; P=0.0002) *(Comi et al 2012)*.
- A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of clinically definite MS with IFN therapy compared to placebo (P<0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFN β-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFN β-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ -1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR=0.6; 95% CI: 0.39 to 0.92; P=0.022).
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining clinically definite MS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to clinically definite MS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; P=0.0087) whereas teriflunomide 7 mg reduced the conversion to clinically definite MS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; P=0.0271).

Progressive MS

- The role of the MS biologic response modifiers in the treatment of primary or secondary progressive MS has not been determined; mitoxantrone is FDA-approved for treating some of these forms of MS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.
- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with primary progressive MS *(Wolinsky et al 2007)*.
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N=3082) of IFN-β compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; P=0.79); however, between-study heterogeneity was high (I^2=57%) *(La Mantia et al 2013)*.

Decisions to discontinue DMTs in MS

- Patient with RRMS eventually progress to secondary progressive MS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for progressive MS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued

therapy vs discontinued therapy for MS in comparable populations. Based on low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFN β-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Low strength evidence from 1 study reported that IFN use did not change disability progression in patients with RRMS. Most patients discontinue MS therapy after 2 or 3 years. Several observational studies have been published on the risks of relapse and rebound of disease activity following the interruption or discontinuation of natalizumab. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy.

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs. placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs. placebo, respectively), closely followed by daclizumab (46%) and natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for pegIFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- RCTs (n=39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegIFNβ-1a, azathioprine and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: Lemtrada, mitoxantrone, Tysabri, and Gilenya were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N=17,897):
    - Lemtrada: RR=0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR=0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - Tysabri: RR=0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - Gilenya: RR=0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - Tecfidera: RR=0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - Zinbryta: RR=0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - Copaxone: RR=0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N=16,800):
    - Lemtrada: RR=0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR=0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - Tysabri: RR=0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - Gilenya: RR=0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N=16,800):
    - mitoxantrone: RR=0.20, 95% CI: 0.05 to 0.84; low quality evidence
    - Lemtrada: RR=0.35, 95% CI: 0.26 to 0.48; low quality evidence
    - Tysabri: RR=0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
  - Acceptability: Higher rates of withdrawal due to AEs compared to placebo over 12 months were reported for Aubagio (RR=2.24, 95% CI: 1.5 to 3.34); Plegridy (RR=2.8, 95% CI: 1.39 to 5.64); Avonex (RR=4.36, 95% CI: 1.98 to 9.6); Rebif (RR=4.83, 95% CI: 2.59 to 9); and Gilenya (RR=8.26, 95% CI: 3.25 to 20.97).
  - Over 24 months, only Gilenya had a significantly higher proportion of participants who withdrew due to any AE (RR vs placebo=1.69, 95% CI: 1.32 to 2.17).
    - mitoxantrone: RR=9.82, 95% CI: 0.54 to 168.84
    - Tysabri: RR=1.53, 95% CI: 0.93 to 2.53
    - Lemtrada: RR=0.72, 95% CI: 0.32 to 1.61

- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N=17,401).
  - On the basis of high quality evidence, Tysabri and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR=0.32, 95% CI: 0.24 to 0.43; OR=0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR=0.28, 95% CI: 0.22 to 0.36; OR=0.19, 95% CI: 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, Tysabri and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Tysabri and Betaseron were significantly more effective (OR=0.62, 95% CI: 0.49 to 0.78; OR=0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, intravenous immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N=16,998) (CADTH, 2013). Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for Tysabri and Lemtrada, 50% for Gilenya or Tecfidera, and 30% for SC IFNs, Copaxone, or Aubagio.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and Gilenya (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for Tecfidera (0.76, 95% CI: 0.62 to 0.93) compared with Copaxone.
  - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, Tysabri, Gilenya, Aubagio, and Tecfidera; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for Tysabri to 0.74 (95% CI: 0.57 to 0.96) for Aubagio. Between-treatment differences were less apparent for risk of sustained disability progression.
  - Among active comparisons, the risk of sustained disability progression was statistically lower for Lemtrada (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
  - Among active comparisons, MRI findings were more favorable for Lemtrada compared with Rebif, and more favorable for all 3 of Gilenya, Betaseron, and Rebif compared with Avonex. Compared with Copaxone, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
  - The incidence of serious AEs and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and Lemtrada.

CLINICAL GUIDELINES

- National treatment guidelines from the American Academy of Neurology (AAN) (published in 2002 and reaffirmed in 2008) stated that on the basis of several consistent Class I studies (ie, prospective RCTs with masked outcome assessments in representative populations), IFNβ has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with CIS who are at high risk of developing MS *(Goodin et al 2002)*. Treatment of MS with IFNβ produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression. As a result, it is appropriate to consider IFNβ for treatment in any patient who is at high risk for developing clinically definite MS (CDMS), or who already has either RRMS or SPMS and is still experiencing relapses. On the basis of Class I evidence, glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS. Treatment with glatiramer acetate produces a beneficial effect on MRI measures of disease severity, such as T2 disease burden, and possibly also slows sustained disability progression in patients with RRMS. As a result, it is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS.
- In a 2008 Disease Management Consensus Statement, the National Clinical Advisory Board of the National Multiple Sclerosis Society stated the following: *(Miller et al 2008)*

- Initiation of treatment with an IFNβ medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS.
- Treatment with mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with SPMS who are worsening, whether or not relapses are occurring.

- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In March 2017, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
  - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
    - Suboptimal treatment response as determined by the individual and his or her treating clinician
    - Intolerable side effects
    - Inadequate adherence to the treatment regimen
    - Availability of a more appropriate treatment option
  - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
  - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
  - Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
    - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
    - Potential contraindications limit options for some individuals.
    - Risk tolerance varies among people with MS and their treating clinicians.
    - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
    - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
  - Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy

including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.

- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, systemic reaction of flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria immediately following injection. Injection site reactions including lipodystrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions.
- Fingolimod was approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination may take up to 2 months so monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Establish immunity to varicella zoster virus prior to therapy initiation. Cases of PML have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. The most common adverse reactions (≥10% and ≥2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. Common adverse events (incidence ≥10% and ≥2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or temporary dose reduction to 120 mg twice daily may reduce flushing.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction to natalizumab. Other warnings with natalizumab include hypersensitivity reactions, increased risk of Herpes encephalitis and meningitis, increased risk of infections, and hepatotoxicity. The most common adverse reactions (incidence ≥ 10%) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, and the possibility of an increased risk of malignancies.

Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab.

- Daclizumab) is contraindicated in patients with pre-existing hepatic disease or hepatic impairment, including serum ALT or aspartate aminotransferase (AST) at least 2 times the upper limit of normal (ULN); history of autoimmune hepatitis or other autoimmune condition involving the liver; and history of hypersensitivity to daclizumab or any other components of the formulation – use in such patients may result in anaphylaxis or life-threatening multi-organ hypersensitivity. Daclizumab carries boxed warnings for hepatic injury including autoimmune hepatitis and other immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and others. Daclizumab is available only through a restricted distribution program called the daclizumab REMS Program.
  - Daclizumab can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. In clinical trials, 1 patient died due to autoimmune hepatitis. Liver injury, including autoimmune hepatitis, can occur at any time during treatment with daclizumab, with cases reported up to 4 months after the last dose of daclizumab. Serum transaminases (ALT and AST) and total bilirubin levels should be tested prior to starting treatment with daclizumab, monthly and before the next dose of daclizumab, and then for 6 months after the last dose of daclizumab. Treatment discontinuation or interruption may be required based on elevations in liver function tests.
  - Overall, serious immune-mediated conditions were observed in 5% of patients treated with daclizumab. If a patient develops a serious immune-mediated disorder, treatment with daclizumab may need to be stopped, and the patient should be referred to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment. Some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of daclizumab.
  - Other warnings and precautions include acute hypersensitivity, infections, and depression and suicide.
  - The most common adverse events (≥ 5% and ≥ 2% higher than comparator) with daclizumab use were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, and lymphadenopathy compared with Avonex; and upper respiratory tract infection, depression, rash, pharyngitis, and increased ALT compared with placebo.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs. 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs. in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017).
  - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse

reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of Ampyra should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). Based on animal data, dalfampridine may cause fetal harm.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure orwait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day,	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone, Glatopa (glatiramer acetate)	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, Glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)†	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if heart rate <45 bpm, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); and a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter). Conduct baseline and yearly	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of two months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			skin exams to monitor for melanoma.	6 weeks prior to treatment with alemtuzumab.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of > 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection	SC	Every 14 days Titration: Start with 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a)	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				treatment days.
Tecfidera (dimethyl fumarate)	Capsules	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Zinbryta (daclizumab)†	Injection	SC	Once a month (every 4 weeks)	Following initial administration by a trained healthcare provider, daclizumab may be self-administered. Sites for injection include the thigh, abdomen, and back of the upper arm. Prior to initiating daclizumab, obtain and evaluate the following: serum transaminases (ALT and AST) and total bilirubin levels. Initiation of daclizumab is contraindicated in patients with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				pre-existing hepatic disease or hepatic impairment including an ALT or AST at least 2 times the upper limit of normal. Avoid initiating daclizumab in patients with tuberculosis or other severe active infection; daclizumab is contraindicated in patients with pre-existing hepatic disease (ie, Hepatitis B or C). Test transaminase levels and total bilirubin monthly and assess before the next dose of daclizumab and follow transaminase levels and total bilirubin monthly for 6 months after the last dose of daclizumab. The interruption or discontinuation of daclizumab therapy is recommended for the management of certain liver test abnormalities; see the package insert for more details.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with RRMS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite RRMS begin DMTs *(MS Coalition 2017)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period following treatment initiation with IFNβ or Copaxone (glatiramer acetate) *(MS Coalition 2017)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy. With IFNβ, use caution in patients with depression or other mood disorders. Peginterferon ß-1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of neutralizing antibody development. Adverse effect profile is similar among the interferons.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Generic glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial biologic response modifier therapy with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or perceived inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor

response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS biologic response modifiers should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015)*. Premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different biologic response modifier *(Coyle 2008, Portaccio et al 2008)*.

- There are now 3 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
- Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
  - In the postmarketing setting, third degree atrioventricular (AV) block and AV block with junctional escape have been observed. Isolated delayed events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. The relationship of these events to fingolimod is uncertain.
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Tysabri (natalizumab) has demonstrated very high efficacy vs. placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). The FDA's update to the labeled indication of Tysabri, with removal of the statement that it is recommended for patients who have had an inadequate response to, or are unable to tolerate an alternate MS therapy, suggests that natalizumab can be considered a first-line agent in RMS, as long as the benefit of higher efficacy is sufficient to offset the risk. Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a second highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The convenient dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Zinbryta (daclizumab) is another option for patients with relapsing forms of MS who are not candidates for natalizumab and/or alemtuzumab. Daclizumab demonstrated statistically significant effects on ARR vs. Avonex and vs placebo, which place it near to or just ahead of the orals, but below the natalizumab level of efficacy. While daclizumab carries boxed warnings for hepatic injury and other immune-mediated disorders (ie, cutaneous reactions), there have been as yet no reported cases of PML.
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.

  - The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

REFERENCES

- Alsop JC for the PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group. Interferon β-1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology*. 2005;65:48-55.
- Ampyra [package insert], Ardsley, NY: Acorda Therapeutics, Inc., October 2016.
- Aubagio [package insert], Cambridge, MA: Genzyme; November 2016.
- Avonex [package insert], Cambridge, MA: Biogen Idec.; March 2016.
- Barbero P, Bergui M, Versino E. Every-other-day interferon beta-1b vs once-weekly interferon ß-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. *Mult Scler*. 2006;12:72-6.
- Betaseron [package insert], Whippany, NJ: Bayer Healthcare Pharmaceuticals; September 2016.
- Butler M, Forte ML, Schwehr N, et al. Decisional Dilemmas in Discontinuing Prolonged Disease-Modifying Treatment for Multiple Sclerosis. Comparative Effectiveness Review No. 150. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 15-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed June 20, 2017.
- Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNβeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology*. 2009;72(23):1976-83.
- Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol*. 2014b;13:657-65.
- Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014a;13(6):545-56.
- Caon C, Din M, Ching W, et al. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2006;13:471-4.
- Carra A, Onaha P, Luetic G. Therapeutic outcome three years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. *Eur J Neurol*. 2008;15:386-93.
- CADTH. Management of relapsing-remitting multiple sclerosis. 2013. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0060853/?report. Accessed June 20, 2017.
- Clerico M, Faggiano F, Palace J, et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane Database Syst Rev*. 2008; (2):CD005278.
- ClinicalTrials.gov Web site. http://clinicaltrials.gov/. Accessed April 4, 2017.
- Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362:402-15.
- Cohen JA, Coles AJ, Arnold DL, et al for the CARE-MS 1 investigators. Alemtuzumab versus interferon beta-1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trials. *Lancet*. 2012;380:1819-28.
- Cohen JA, Khatri B, Barkhof F, et al for the TRANSFORMS (TRial Assessing injectable interferon vS. FTY720 Oral in RRMS) Study Group. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomized TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2015;0:1–8.
- Coles AJ, Twyman CL, Arnold DL, et al for the CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomized controlled phase 3 trial. *Lancet*. 2012;380:1829-39.
- Comi G, Cohen JA, Arnold DL, et al for the FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol*. 2011;69(1):75-82.
- Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. *Mult Scler*. 2012;19(8):1074-1083.
- Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9700):1503-11.

- Confavreux C, O'Connor P, Comi G, et al for the TOWER trial group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:247-56.
- Copaxone [package insert], Overland Park, MO: Teva Neuroscience Inc.; September 2016.
- Corboy JR, Halper J, Langer-Gould AM, et al. Position Statement: Availability of Disease Modifying Therapies (DMT) for the Treatment of Relapsing Forms of Multiple Sclerosis. 2015. https://www.aan.com/uploadedFiles/Website_Library_Assets/Documents/6.Public_Policy/1.Stay_Informed/2.Position_Statements/DiseaseModTheraMS_PosStatement.pdf. Accessed June 20, 2017.
- Coyle PK. Switching algorithms: from one immunomodulatory agent to another. *J Neurol*. 2008; 255(Suppl 1):44-50.
- Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value (Final Evidence Report; March 6, 2017). Prepared for the California Technology Assessment Forum by the Institute for Clinical and Economic Review (ICER). ICER Web site. https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf. Accessed May 31, 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 7, 2017.
- Durelli L, Verdun E, Barbero P. Every-other-day interferon beta-1b vs once-weekly interferon ß-1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). *Lancet*. 2002;359:1453-60.
- Edan G, Kappos L, Montalban X et al for the BENEFIT Study Group. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry*. 2014;85:1183–1189.
- Extavia [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; May 2016.
- FDA Grants Priority Review for Genentech's OCREVUS™ (Ocrelizumab) Biologics License Application. Genentech Press Release June 27, 2016. https://www.gene.com/media/press-releases/14631/2016-06-27/fda-grants-priority-review-for-genentech. Accessed March 21, 2017.
- FDA Center for Drug Evaluation and Research. Approval letter for BLA 761053. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761053Orig1s000ltr.pdf. Accessed April 3, 2017.
- Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2013, Issue 6. Art. No.: CD008933.
- Flechter S, Vardi J, Rabey JM. Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaseron®) in multiple sclerosis patients: an open-label 2-year follow-up. *J Neurol Sci*. 2002;197:51-5.
- Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord*. 2016;9:23-30.
- Fox RJ, Miller DH, Phillips T, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367:1087-97.
- Freedman MS, Hughes B, Mikol DD, et al. Efficacy of disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic comparison. *Eur Neurol*. 2008;60(1):1-11.
- Freedman MS, Selchen D, Arnold DL, et al for the Canadian Multiple Sclerosis Working Group. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. *Can J Neurol Sci*. 2013;40:307-323.
- Frohman EM, Shah A, Eggenberger E, et al. Corticosteroids for multiple sclerosis: I. Application for treating exacerbations. *Neurotherapeutics*. 2007;4(4):618–626.
- Garnock-Jones KP. Alemtuzumab: a review of its use in patients with relapsing MS. *Drugs.* 2014;74:489-504.
- Gilenya [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2016.
- Giovannoni G, Gold R, Selmaj K, et al; SELECTION Study Investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. *Lancet Neurol*. 2014;13(5):472-81.
- Glatopa [package insert], Princeton, NJ: Sandoz Inc.; April 2016.
- Gold R, Giovannoni G, Selmaj K, et al; SELECT study investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;381(9884):2167-75.
- Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367:1098-107.
- Gold R, Radue EW, Giovannoni G, et al. Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. *BMC Neurol*. 2016;16:117.
- Goodin DS, Frohman EM, Garmany GP. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-78.
- Goodin DS, Frohman EM, Hurwitz B. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(13):977-84.
- Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFN β-1b trial. *Neurology*. 2012;78:1315–1322.
- Goodman AD, Brown TR, Krupp LB et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. *Lancet.* 2009;373:732-38.
- Govindappa K, Sathish J, Park K, et al. Development of interferon beta-neutralizing antibodies in multiple sclerosis – a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2015;71:1287-1298.
- Hartung HP, Gonsette R, Konig N, et al for the Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomized, multicenter trial. *Lancet*. 2002;360(9350):2018-25.
- Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234.
- Jacobs LD, Cookfair DL, Rudick RA, et al for The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon ß-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol*. 1996;39:285-294.
- Jensen HB, Ravnborg M, Dalgas U, et al. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. *Ther Adv Neurol Disord.* 2014;7(2):97-113.

- Johnson KP, Brooks BR, Cohen JA, et al for the Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology*. 1995;45: 1268-1276.
- Kappos L, Freedman MS, Polman CH, et al for the BENEFIT Study Group. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT Study. *Lancet*. 2007;370:389-97.
- Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet*. 2011;378(9805):1779-87.
- Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.
- Kappos L, Traboulsee A, Constantinescu C. Long-term subcutaneous interferon ß-1a therapy in patients with relapsing-remitting MS. *Neurology*. 2006;67:944-53.
- Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med*. 2015;373(15):1418-28.
- Khan O, Rieckmann P, Boyko A, et al for the GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol*. 2013;73:705-713.
- Khan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effects of IFNβ-1a (Avonex), IFNβ-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Mult Scler*. 2001b;7:349-53.
- Khan OA, Tselis AC, Kamholz JA. A prospective, open-label treatment trial to compare the effect of IFN β-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2001a;8:141-8.
- Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon ß-1a in relapsing-remitting multiple sclerosis: a randomized extension of the TRANSFORMS study. *Lancet Neurol*. 2011 Jun;10(6):520-9.
- Kieseier BC, Arnold DL, Balcer LJ et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler*. 2015
- Jul;21(8):1025-35.
- Kinkel RP, Dontchev M, Kollman C, et al for the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance Investigators. Association between immediate initiation of intramuscular interferon ß-1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. *Arch Neurol*. 2012;69(2):183-90.
- Krapf H, Morrissey SP, Zenker O, et al for the MIMS Study Group. Effect of mitoxantrone on MRI in progressive MS: results of the MIMS trials. *Neurology*. 2005;65(5):690-5.
- La Mantia L, Di Pietrantonj C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2016;11:CD009333.
- La Mantia L, Vacchi L, Rovaris M, et al. Interferon β for Secondary Progressive Multiple Sclerosis: A Systematic Review. *J Neurol Neurosurg Psychiatry*. 2013; 84(4):420-426.
- Lemtrada [package insert], Cambridge, MA: Genzyme Corporation; July 2016.
- Limmroth V, Malessa R, Zettl UK. Quality assessments in multiple sclerosis therapy (QUASIMS). *J Neurol*. 2007;254:67-77.
- Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol*. 2013;73:327-340.
- Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-86.
- Marriott JJ, Miyasaki JM, Gronseth G, et al for Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(18):1463-70.
- McGinley MP, Moss BP, Cohen JA. Safety of monoclonal antibodies for the treatment of multiple sclerosis. *Expert Opin Drug Saf*. 2017;16(1):89-100.
- Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous acetate in patients with relapsing multiple sclerosis (the Rebif vs Glatiramer acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial. *Lancet Neurol*. 2008;7:903-14.
- Miller A, Cohen B, Cohen J, et al. National Clinical Advisory Board of the National Multiple Sclerosis Society. MS Disease Management Consensus Statement. 2008. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Disease-Management-Consensus-Statement-(under-revision).pdf. Accessed June 20, 2017.
- Miller AE, Wolinsky JS, Kappos L, et al for the TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-86.
- Miller DH, Chard DT, Ciccarelli O. Clinically Isolated Syndromes. *Lancet Neurol*. 2012;11(2):157-69.
- Minagara A, Murray TJ. Efficacy and tolerability of intramuscular interferon ß-1a compared to subcutaneous interferon ß-1a in relapsing MS: results from PROOF. *Curr Med Res Opin*. 2008; 24(4):1049-55.
- Miravelle AA. Guidelines and best practices for appropriate use of dalfampridine in managed care populations. *Am J Manag Care.* 2011;17:S154-S160.
- Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220.
- MS Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. Updated March 2017. http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed May 5, 2017.
- Mitoxantrone [package insert], Irvine, CA: Teva Parenteral Medicines, Inc.; May 2012.
- National Multiple Sclerosis Society, 2014a. Overview of Relapsing-remitting MS (RRMS). http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed June 20, 2017.
- National Multiple Sclerosis Society, 2014b. Who Gets MS? http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed June 20, 2017.
- Novantrone [package insert], Rockland, MA: EMD Serono; March 2012.
- O'Connor P, Filippi M, Arnason B, et al. 250 mcg or 500 mcg interferon beta-1b vs 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomized, multicentre study. *Lancet Neurol*. 2009 Oct;8(10):889-97.

- O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006;66:894-900.
- O'Connor P, Wolinsky JS, Confavreux C, et al for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365:1293-303
- Ocrevus [dossier], South San Francisco, CA: Genentech, Inc.; 2017.
- Ocrevus [package insert], South San Francisco, CA: Genentech, Inc.; March 2017.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 7, 2017.
- Panitch H, Goodin D, Francis G. Benefits of high-dose, high-frequency interferon ß-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *J Neurol Sci*. 2005;239:67-74.
- Panitch H, Goodin D, Francis G. Randomized, comparative study of interferon ß-1a treatment regimens in MS: the EVIDENCE trial. *Neurology*. 2002;59:1496-506.
- Plegridy [package insert], Cambridge, MA: Biogen Idec.; July 2016.
- Polman CH, O'Connor PW, Havrdova, et al for the AFFIRM Study Investigators. Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006; 354:899-910.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.
- Portaccio E, Zipoli V, Siracusa G, et al. Long-term adherence to interferon β therapy in relapsing-remitting multiple sclerosis. *Eur Neurol*. 2008;59:131-5.
- PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352:1498-504.
- Pucci E, Giuliani G, Solari A, et al. Natalizumab for relapsing remitting multiple sclerosis (Review). *Cochrane Database Syst Rev*. 2011;(10):CD007621.
- Rebif [package insert], Rockland, MA: EMD Serono; November 2015.
- Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years' experience in a specialist multiple sclerosis centre. *J Neurol*. 2005;252:795-800.
- Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. *Neurology*. 2004;63(12 Suppl 6):S8-14.
- Ruck T, Bittner S, Simon OJ et al. Long-term effects of dalfampridine in patients with multiple sclerosis. *J Neurol Sci.* 2014;337(1-2):18-24.
- Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus Interferon ß-1a for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:911-23.
- Sanvito L, Constantinescu CS, Gran B. Novel therapeutic approaches to autoimmune demyelinating disorders. *Curr Pharm Des*. 2011;17(29):3191-201.
- Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly vs high dose, high-frequency interferon β-1a for relapsing multiple sclerosis. *Clin Ther*. 2007;29(9):2031-48.
- Schwid SR, Thorpe J, Sharief M. Enhanced benefit of increasing interferon ß-1a dose and frequency in relapsing multiple sclerosis. The EVIDENCE study. *Arch Neurol*. 2005;62:785-92.
- Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) Guidelines for Prescribing Disease-Modifying Treatments in Multiple Sclerosis. http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139. Accessed June 20, 2017.
- Sorensen PS, Deisenhammer F, Duda P, et al for the EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. *Eur J Neurol*. 2005;12(11):817-27.
- Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. *Ther Adv Neurol Disord*. 2016;9(1):44-52.
- Tecfidera [package insert], Cambridge, MA: Biogen Idec Inc.; January 2017.
- The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-lb in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. *Neurology*. 1995;45:1277-1285.
- The IFNB Multiple Sclerosis Study Group. Interferon beta-lb is effective in relapsing-remitting - multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655-661.
- Traboulsee A, Sabbagh AL, Bennett R, et al. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting sclerosis: analysis of 48-week data from the EVIDENCE (evidence of interferon dose-response: European North American comparative efficacy) study. *BMC Neurol*. 2008;8:11.
- Tramacere I, DelGiovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2015, Issue 9. Art. No.: CD011381.
- Trojano M, Liguori M, Paolicelli D. Interferon beta in relapsing-remitting multiple sclerosis: an independent post marketing study in southern Italy. *Mult Scler*. 2003;9:451-7.
- Trojano M, Pellegrini F, Fuiani A. New natural history of interferon-beta-treated relapsing multiple sclerosis. *Ann Neurol*. 2007;61:300-6.
- Tysabri [package insert], Cambridge, MA: Biogen Idec Inc.; May 2016.
- Vermersch P, Czlonkowska A, Grimaldi LME, et al for the TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Sclerosis Journal*. 2014;20(6):705-716.
- White JT, Kieseier BC, Newsome SD, et al. Immunogenicity with peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the randomized phase 3, multicenter ADVANCE study in relapsing-remitting multiple sclerosis (EP4152). *Eur J Neurol*. 2014;21(Suppl 1):104-387 [abstract].
- Wingerchuk DM, and Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clin Proc*. 2014;89(2):225-240.

- Wolinsky JS, Narayana PA, O'Connor P. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol*. 2007;61:14-24.
- Xu Z, Zhang F, Sun F, et al. Dimethyl fumarate for multiple sclerosis. *Cochrane Database Syst Rev*. 2015, Issue 4. Art. No.: CD011076.
- Zinbryta [package insert], Cambridge, MA: Biogen Inc.; May 2017.
- Zwibel HL. Glatiramer acetate in treatment-naïve and prior interferon b-1b-treated multiple sclerosis patients. *Acta Neurol Scand*. 2006;113:378-86.

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Therapeutic Class Overview
Cholesterol Absorption Inhibitors

INTRODUCTION

- There are several classes of medications used to alter lipids, including the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants, omega-3 fatty acids, and nicotinic acid (niacin). Each medication class differs with respect to the mechanism by which they alter lipids, as well as to what degree; therefore, Food and Drug Administration (FDA)-approved indications for a particular medication class are influenced by the underlying lipid abnormality.
- In addition to the medication classes mentioned above, the cholesterol absorption inhibitor Zetia (ezetimibe) is also effective in the management of hypercholesterolemia and has a unique mechanism of action compared to the other available treatments. Specifically, this agent works to reduce blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol, which results in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately, lower systemic cholesterol levels. Ezetimibe is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia.
- The role of ezetimibe in the management of hypercholesterolemia is not well established. It is primarily used as monotherapy or in combination with a statin. In patients already receiving a statin, maximizing the statin dose can achieve similar reductions in low density lipoprotein cholesterol (LDL-C) as adding ezetimibe to treatment. The addition of ezetimibe may be helpful in avoiding high doses of statins *(Smith et al 2011).*
- Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain essential modalities in the management of patients with hypercholesterolemia (*Eckel et al 2013, Canoniero et al 2017).* In general, the statins are considered first line therapy for decreasing LDL-C levels (*Canoniero et al 2017, Perk et al 2012, Stone 2013*). If after 4 to 12 weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a nonstatin therapy should be considered (*Stone 2013).*
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focuses more heavily on a patient's overall atherosclerotic cardiovascular disease (ASCVD) risk versus achieving target LDL-C and/or non-high density lipoprotein cholesterol (non-HDL-C) levels to guide appropriate treatment. The guideline also states that adherence to lifestyle modifications and to statin therapy should be re-emphasized before considering the addition of a non-statin drug such as ezetimibe (*Stone et al 2013).* Updated 2016 ACC guidance recommends ezetimibe as the first-line non-statin option for most patient scenarios (*Lloyd-Jones et al 2016).*

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Zetia (ezetimibe)	✔

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Zetia (ezetimibe)
Homozygous Familial Hypercholesterolemia	
In combination with atorvastatin or simvastatin to reduce elevated total cholesterol and low density lipoprotein cholesterol levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid lowering treatments (e.g., low density lipoprotein apheresis) or if such treatments are unavailable.	✔
Homozygous Sitosterolemia	
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.	✔
Primary Hyperlipidemia	
Adjunctive therapy to diet for the reduction of elevated total cholesterol, low density	✔

Indications	Zetia (ezetimibe)
lipoprotein cholesterol, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia.	
Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol with primary (heterozygous familial and non-familial) hyperlipidemia.	✔
Adjunctive therapy in combination with fenofibrate to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B and non-high density lipoprotein cholesterol in adult patients with mixed hyperlipidemia.	✔

(*Zetia prescribing information 2013)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.
- In December 2015, the FDA's Endocrinologic and Metabolic Advisory Committee met to discuss Merck's application for a label update to be applied to all ezetimibe-containing products. Based on results from the IMPROVE-IT trial, the proposed indication was ezetimibe in combination with a statin are indicated to reduce the risk of cardiovascular (CV) events in patients with coronary heart disease (CHD). The FDA advisory panel voted 10-5 against expanding the use of ezetimibe plus statin therapy for the reduction of CV events in patients with CHD. A few of those reasons cited in the FDA transcript included:
  - Many panel members were not convinced that the IMPROVE-IT trial results were clinically robust. Effect was small even before considering the issues regarding missing observation time.
  - Those high risk subgroups which demonstrated improved benefit, including diabetics and patients aged ≥ 75 years, were promising, but some members felt these results were currently at the point of hypothesis.
  - Some felt "CHD" was too broad for the population studied within the IMPROVE-IT trial.
  - Overall safety was generally favorable and not concerning, but some panelists expressed concerns over the small but troubling risk for hemorrhagic stroke in the ezetimibe group.
- The FDA issued a complete response letter rejecting Merck's application for a secondary-prevention indication for ezetimibe-containing products *(FDA transcript 2015).*

CLINICAL EFFICACY SUMMARY

- In clinical trials, ezetimibe consistently demonstrated superiority over placebo in the management of hypercholesterolemic conditions. Ezetimibe significantly lowered total cholesterol (TC), LDL-C, Apo B, non-HDL-C, and triglycerides (TG), and increased HDL-C compared to placebo in clinical studies ranging in length from 8 to 26 weeks *(Dujovne et al 2002, Gonzalez-Ortiz et al 2006, Kalogirou et al 2007, Knopp et al 2003, Musliner et al 2008, Salen et al 2004, Wierzbicki et al 2005).*
- In line with treatment guidelines, study results also demonstrated that the addition of a cholesterol absorption inhibitor to a statin has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents alone *(Ballantyne et al 2003, Bays et al 2004, Chenot et al 2007, Constance et al 2007, Feldman et al 2004, Feldman et al 2006, Goldberg et al 2004, Goldberg et al 2006, Hing Ling et al 2012, Kerzner et al 2003, Okada et al 2011, Ose et al 2007, Pearson et al 2007, Stein et al 2004, Stojakovic et al 2010).*
- In addition, when a cholesterol absorption inhibitor was combined with fenofibrate, significant reductions in LDL-C, TG and TC were observed as compared to either therapy alone *(Ansquer et al 2009, Farnier et al 2005, McKenney et al 2006)*.
- The ODYSSEY Mono trial compared the cholesterol absorption inhibitor to the fully human monoclonal antibody against proprotein convertase subtilisin/kexin 9 (PCSK9) alirocumab. It was a 24-week, Phase 3, randomized, double-blind (DB), active-controlled (AC), double-dummy trial of male and female patients aged ≥ 18 years with a 10-year risk of fatal CV events of ≥ 1% and < 5%, based on the European Systematic Coronary Risk Estimation. Patients were not receiving statin or any other lipid-lowering therapy for at least four weeks prior to screening and were randomized (permuted-block design) in a 1:1 ratio to receive either ezetimibe 10 mg/day orally plus SC placebo every 2 weeks (n=51) or alirocumab 75 mg SC every 2 weeks plus oral placebo daily (n=52). The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks. Mean baseline LDL-C levels were 141.1 mg/dL in the alirocumab arm and 138.3 mg/dL

in the ezetimibe arm. For the primary efficacy analysis, least-squares (LS) mean (standard error [SE]) percent reductions in LDL-C from baseline to week 24 were 47 (3)% in the alirocumab group vs. 16 (3)% in the ezetimibe group, with a statistically significant LS mean (SE) difference between groups of 32 (4)% ($p < 0.0001$). Alirocumab demonstrated tolerability and safety comparable with ezetimibe. Alirocumab demonstrated superior efficacy in monotherapy compared with ezetimibe over 24 weeks of treatment *(ClinicalTrials.gov NCT01644474 2014; Roth et al 2014*). A pooled analysis of eight ODYSSEY clinical trials of up to 104 weeks in high-risk patients receiving background statin therapy found that alirocumab reduced LDL-C levels to a significantly greater degree than both ezetimibe and placebo in various pooled analyses, with results sustained up to week 104 *(Farnier et al 2016).*

- The GAUSS-3 trial compared PCSK9 inhibitor evolocumab to ezetimibe in a 24-week, Phase 3, randomized, DB, AC, double-dummy trial of patients who had a history of intolerance to ≥ 2 statins. At baseline, patients had a mean age of 61 years, 34.6% had CHD, and a mean LDL-C level of 212.3 mg/dL. Patients were administered atorvastatin 20 mg/day and placebo in a 24 week crossover period, in which 42.6% developed muscle symptoms while taking atorvastatin but not while taking placebo. A total of 218 patients were randomized (1:2) to ezetimibe 10 mg/day (n=73) or evolocumab 420 mg/month (n=145). Evolocumab significantly outperformed ezetimibe for the co-primary end points of mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels (between group mean percent change difference, -37.8%) and from baseline to week 24 levels (ezetimibe, -16.7%; 95% CI, -20.5% to -12.9% vs. evolocumab, -54.5%; 95% CI, 57.2% to 51.8%; $p < 0.001$). At 24 weeks, there were no differences between groups in muscle symptoms (ezetimibe, 28.8% vs. evolocumab, 20.7%; $p = 0.17$). Evolocumab was associated with reduced TC and Apo B levels and increased HDL-C levels ($p < 0.005$ for each), but no significant differences in TG or very low-density lipoprotein cholesterol (VLDL-C) levels (*Nissen et al 2016).*
- A meta-analysis that compared PCSK9 inhibitors to ezetimibe (2 randomized controlled trials [RCTs]) and ezetimibe and statins (5 RCTs) found an LDL-C reduction of 30.2% (95% CI, 34.18 to 26.23) with PCSK9 inhibitors compared to ezetimibe alone and a reduction of 39.2% (95% CI, 56.15 to 22.26) compared to ezetimibe plus statins. The risk difference (RD) for risk of cardiovascular disease events (3 RCTs) was 1.06% (OR 0.45; 95% CI, 0.27 to 0.75) with PCSK9 inhibitors compared to ezetimibe plus statins; however, the data was of very low quality so the finding was considered to have considerable uncertainty. Risk of adverse events (4 RCTs) were increased with PCSK9 inhibitors compared to ezetimibe plus statins (RD, 3.7%; OR, 1.18; 95% CI, 1.05 to 1.34) *(Schmidt et al 2017).*
- The IMPROVE-IT trial was a multi-center (MC), DB, placebo-controlled (PC), RCT in 18,144 patients designed to assess CV outcomes through the addition of ezetimibe 10 mg to simvastatin 40 mg compared to simvastatin 40 mg alone in patients hospitalized with acute coronary syndromes. After a median of 6 years, patients randomized to ezetimibe/simvastatin had a 6.4% relative risk reduction (or approximately a 2% absolute reduction) of CV events (defined as a composite of CV death, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke) compared with those who received simvastatin alone (HR, 0.94; 95% CI, 0.89 to 0.99; $p = 0.016$). There were no significant differences in adverse events *(Cannon et al 2015).*
- The PRECISE-IVUS trial evaluated ezetimibe with atorvastatin compared with atorvastatin monotherapy in patients who had undergone a percutaneous coronary intervention. Combination therapy resulted in significantly better coronary plaque regression and significantly lower LDL-C levels than monotherapy *(Tsujita et al 2015).*
- One study evaluated the safety and efficacy of ezetimibe in children aged 6 to 10 years with heterozygous familial hypercholesterolemia (ezetimibe is approved for children aged 10 to 17 years) for 12 weeks. Total cholesterol, non-HDL, and Apo-B were all significantly reduced with ezetimibe compared to placebo, and safety was similar to that seen in other studies with older children and adults *(Kusters et al 2015).* One systematic review in children and adolescents with heterozygous familial hypercholesterolemia included evidence as it related to treatment with ezetimibe. In one trial of 248 patients, ezetimibe with simvastatin resulted in greater LDL-C reductions compared with simvastatin monotherapy after 33 weeks (mean, -54% vs. -38.1% [standard deviation, 1.4% for each group]). One trial of ezetimibe monotherapy (n = 138) demonstrated mean LDL-C decreases of 28% (95% CI, -31% to -25%) from baseline and a negligible change with placebo after 12 weeks (*Lozano et al 2016).*

CLINICAL GUIDELINES

- Current treatment guidelines recognize ezetimibe monotherapy or in combination with statin therapy as an LDL-C lowering option *(Canoniero et al 2017, Cuchel et al 2014, Jellinger et al 2017, Lloyd-Jones et al 2016, Stone et al 2013).*
  - In 2016, the American College of Cardiology issued expert consensus pathway guidance for non-statin therapy in ASCVD due to gaps in current evidence. Ezetimibe is acknowledged as the first non-statin medication that should be considered in most patient scenarios. Bile acid sequestrants may be considered second-line for certain patients who

do not tolerate ezetimibe. PCSK9 inhibitors may be considered in higher-risk patients with clinical ASCVD or familial hypercholesterolemia if goals of therapy have not been achieved on maximally tolerated statin and ezetimibe *(Lloyd-Jones et al 2016).*

- The objective of the Synopsis of the Kidney Disease: Improving Global Outcomes (KDIGO) 2013 Clinical Practice Guideline on Lipid Management in Chronic Kidney Disease (CKD) is to offer guidance on the management of dyslipidemia and use of cholesterol lowering medications in all adults and children with known CKD (defined by reduced estimated glomerular filtration rate [eGFR] or markers of kidney damage, such as abnormal albuminuria). A key element was the recommendation for statin or combination statin/ezetimibe treatment of adults aged 50 years or older with eGFR rates < 60 mL/min/1.73m^2 but not treated with chronic dialysis or kidney transplantation (*Tonelli et al 2013).*

SAFETY SUMMARY

- Ezetimibe, administered alone or with statin, is generally well tolerated. For ezetimibe monotherapy, adverse events that were reported at a frequency ≥ 2% and exceeding placebo included diarrhea, fatigue, upper respiratory tract infection, sinusitis, influenza, arthralgia, and pain in extremity.
- Ezetimibe is contraindicated for use in combination with a statin in patients with active liver disease or unexplained persistent elevations in liver enzymes.
- Cyclosporine may significantly increase ezetimibe serum concentrations. In addition, ezetimibe can increase cyclosporine serum concentrations.
- Ezetimibe serum concentrations may be decreased by the concomitant administration of the bile acid sequestrants.
- The use of ezetimibe with a specific statin or fenofibrate should be in accordance with the prescribing information of that product. When administered with a statin, assessment of liver function should be performed at baseline and according to the statin prescribing information.
- Ezetimibe is Pregnancy Risk Factor C. Adverse events were observed in some animal reproduction studies. Use is contraindicated in pregnant women who require combination therapy with a statin.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zetia (ezetimibe)	Tablets	oral	Daily	FDA approved for use in children ages 10 to 17 for the treatment of heterozygous familial hypercholesterolemia.

See the current prescribing information for full details

CONCLUSION

- Ezetimibe is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia. Ezetimibe has a unique mechanism of action and reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.
- The results from clinical trials consistently demonstrate that ezetimibe is safe and effective for the management of lipid disorders, whether as monotherapy or in combination with a statin or fenofibrate.
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle modifications and to statin therapy before considering the addition of a non-statin drug (*Stone et al 2013).* Recent 2016 ACC expert consensus guidance recommends ezetimibe as the first-line non-statin medication for most patient scenarios *(Lloyd-Jones et al 2016).*
- Ezetimibe is available as a branded or generic 10 mg tablet that is administered once daily. The role of ezetimibe in the management of hypercholesterolemia has not been well established. The primary role of ezetimibe has been as add-on therapy with a statin. The statins are considered first-line therapy in the management of hypercholesterolemia as a result of their ability to reduce LDL-C.
- Ezetimibe may be helpful for avoiding high doses of statins in patients who are unable to achieve their lipid goals on low- to moderate-dose statin therapy. Additional clinical trials are warranted to further establish the place of ezetimibe in therapy.

REFERENCES

- Ansquer JC, Bekaert I, Guy M, et al. Efficacy and safety of coadministration of fenofibrate and ezetimibe compared to each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome. *Am J Cardiovasc Drugs*. 2009;9(2):91-101.
- Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation*. 2003 May 20;107(19):2409-15.
- Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther*. 2004 Nov;26(11):1758-73.
- Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). *N Engl J Med*. 2015;372(25):2387-2397.
- Canoniero M, Kottke T, Baechler C, et al. Institute for Clinical Systems Improvement. Lipid Management in Adults. Updated February 2017. Available at: https://www.icsi.org/_asset/qz5ydq/LipidMgmt-Interactive1111.pdf. Accessed May 15, 2017.
- Chenot F, Montant PF, Marcovitch O, et al. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. *Eur J Clin Invest*. 2007 May;37(5):357-63.
- ClinicalTrials.gov NCT01644474. Efficacy and safety of alirocumab SAR236553 (REGN727) versus ezetimibe in patients with hypercholesterolemia (ODYSSEY Mono). Last updated October 7, 2015. Available at: http://clinicaltrials.gov/show/NCT01644474. Accessed May 15, 2017.
- Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2007 Jul;9(4):575-84.
- Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35:2146-57.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 15, 2017.
- Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol*. 2002 Nov 15;90(10):1092-7.
- Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960-84.
- Farnier M, Freeman MW, Macdonell G, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J*. 2005; 26:897-905.
- Farnier M, Gaudet D, Valcheva V, et al. Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials. *Int J Cardiol*. 2016;223:750-757.
- Feldman T, Koren M, Insull W Jr, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. *Am J Cardiol*. 2004 Jun 15;93(12):1481-6.
- Feldman T, Davidson M, Shah A, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post hoc analysis of subpopulations from three pooled clinical trials. *Clin Ther.* 2006 Jun;28(6):849-59.
- Food and Drug Administration (FDA) transcript. Zetia and Vytorin proposed indication: IMPROVE-IT study. Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting. December 14, 2015. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM484886.pdf. Accessed May 15, 2017.
- Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. *Mayo Clin Proc*. 2006 Dec;81(12):1579-88.
- Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2004 May;79(5):620-9.
- Gonzalez-Ortiz M, Martinez-Abundis E, Kam-Ramos AM, et al. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. *Cardiovasc Drugs Ther*. 2006:20(2):143-6.
- Hing Ling PK, Civeira F, Dan AG, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. *Lipids Health Dis.* 2012 Jan 31;11:18.
- Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract.* 2017;23 Suppl 2:1-87.
- Kalogirou M, Tsimihodimos V, Gazi I, et al. Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidaemia. *Curr Med Res Opin*. 2007 May; 23(5):1169-76.
- Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol*. 2003 Feb 15;91(4):418-24.
- Knopp RH, Dujovne CA, Le Beaut A, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolemia: a pooled analysis from two controlled phase III clinical studies. *Int J Clin Pract*. 2003 Jun;57(5):363-8.
- Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. *J Pediatr*. 2015;166(6):1377-1384.e1-3.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2016 Jul 5;68(1):92-125.
- Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: A systematic evidence review for the U.S. Preventive Services Task Force. *JAMA*. 2016 Aug 9;316(6):645-55.
- McKenney JM, Farnier M, Lo KW, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol.* 2006 Apr 18;47(8):1584-7.

- Musliner T, Cselovszky D, Sirah W, et al. Efficacy and safety of ezetimibe 40 mg vs ezetimibe 10 mg in the treatment of patients with homozygous sitosterolemia. *Int J Clin Pract*. 2008 Jul;62(7):995-1000.
- Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016 Apr 19;315(15):1580-90.
- Okada K, Kimura K, Iwahashi N, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. *Circ J*. 2011 Sep 22;75(10):2496-504.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 15, 2017.
- Ose L, Johnson-Levonas A, Reyes R, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. *Int J Clin Pract*. 2007 Sep;61(9):1469-80.
- Pearson T, Ballantyne C, Sisk C, et al. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. *Am J Cardiol*. 2007 Jun 15;99(12):1706-13.
- Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol.* 2012 Aug;19(4):585-667.
- Roth EM, Taskinen MR, Ginsberg HM, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24-week, double-blind, randomized Phase 3 trial. *Int J Cardiol*. 2014;176:55-61.
- Salen G, von Bergmann K, Lutjohann D, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation.* 2004;109:966-71.
- Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;4:CD011748.
- Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J.* 2004 Sep;447-55.
- Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol.* 2011 Nov 29;58(23):2432-46.
- Stojakovic T, de Campo A, Scharnagl H, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. *Eur J Clin Invest*. 2010;40(3):187-94.
- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-45.
- Tonelli M, Wanner C, for the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline. *Ann Intern Med*. 2014 Feb 4;160(3):182.
- Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. *J Am Coll Cardiol*. 2015;66(5):495-507.
- Wierzbicki AS, Doherty E, Lumb PJ, et al. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidemias. *Curr Med Res Opin*. 2005;21(3):333-8.
- Zetia prescribing information. Merck & Co. Inc. Whitehouse Station, NJ. August 2013.

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Therapeutic Class Overview
Statins (HMG-CoA Reductase Inhibitors)

INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.
- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (Stone et al, 2013).
- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).
- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- The combinations niacin/lovastatin (ADVICOR®) and niacin/simvastatin (SIMCOR®) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (AbbVie, 2016).
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALTOPREV (lovastatin extended-release)	Covis Pharma	06/26/2002	-
CRESTOR (rosuvastatin)	AstraZeneca Pharmaceuticals	08/12/2003	✔
LESCOL (fluvastatin)	Novartis	12/31/1993	✔
LESCOL XL (fluvastatin extended-release)	Novartis	10/06/2000	✔
LIPITOR (atorvastatin)	Pfizer.	12/17/1996	✔
LIVALO® (pitavastatin)	Kowa Company	08/03/2009	✔
MEVACOR (lovastatin)*	Merck & Co., Inc	08/31/1987	✔
PRAVACHOL (pravastatin)	Bristol Myers Squibb Company	10/31/1991	✔
ZOCOR (simvastatin)	Merck & Co., Inc.	12/31/1991	✔
CADUET (amlodipine/ atorvastatin)	Pfizer	01/30/2004	✔
LIPTRUZET†	Watson Labs Teva	04/26/2017	✔

Drug	Manufacturer	FDA Approval Date	Generic Availability
(ezetimibe/atorvastatin)			
VYTORIN® (ezetimibe/simvastatin)	Merck & Co., Inc.	07/23/2004	✔

*The brand, MEVACOR, has been discontinued.
†The brand, LIPTRUZET, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was recently approved by the FDA.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-approved Indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ atorvastatin	ezetimibe/ simvastatin
Hypertriglyceridemia										
Reduce elevated TG in patients with hypertriglyceridemia	✔				✔		✔	✔ (atorvastatin)		
Treatment of adult patients with hypertriglyceridemia in combination with diet						✔				
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apo B), and TG and to increase HDL-C in patients with primary hyperlipidemia or hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and very high LDL-C in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B in adults with HoFH						✔				
Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies						✔ ₳				
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ § (IR)							

Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorvastatin)		
Prevention of CVD										
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔				
Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN	✔							✔ (atorvastatin)		
Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)		
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔					
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔				
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD					✔					

Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease							✔			
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD		✔								
Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels			✔							
Other										
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)		
Symptomatic treatment of chronic stable angina								✔ (amlodipine)		
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)		
Treatment of HTN, to lower blood pressure								✔ (amlodipine)		

Abbrv: CAD=coronary artery disease, CHD=coronary heart disease, ER=extended-release, IR=immediate-release, HTN=hypertension, MI=myocardial infarction.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescents girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients eight to 17 years of age
~~A~~In children and adolescents ages seven to 17
ɣFor ER lovastatin, for patients at high risk; for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C

(Prescribing information: ALTOPREV®, 2016; CADUET®, 2017; CRESTOR®, 2016; LESCOL®, 2012; LESCOL XL®, 2012; LIPITOR®, 2017; LIVALO®, 2016; MEVACOR®, 2014; PRAVACHOL®, 2017; VYTORIN®, 2016; ZOCOR®, 2015)
Clinical Pharmacology, 2017

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Numerous clinical trials have demonstrated that the statins (single-entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol (TC), and TG, as well as positively impact other lipid/lipoprotein parameters. Additionally, many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens (Ai et al, 2008; Alvarez-Sala et al, 2008; Arca et al, 2007; Avis et al, 2007; Avis et al, 2010; Ballantyne et al, 2003; Ballantyne et al, 2004; Ballantyne et al, 2005; Ballantyne et al, 2006; Ballantyne et al, 2007; Ballantyne et al, 2008; Bardini et al, 2010; Bays et al, 2004; Bays et al, 2010; Bays et al, 2013; Bays et al, 2008a; Bays et al, 2008b; Becker et al, 2008; Betteridge et al, 2007a; Betteridge et al, 2007b; Braamskamp et al, 2015; Brown et al, 1990; Bullano et al, 2006; Bullano et al, 2007; Calza et al, 2008; Catapano et al, 2006; Charland et al, 2010; Chenot et al, 2007; Clearfield et al, 2006; Coll et al, 2006; Conard et al, 2008; Constance et al, 2007; Davidson et al, 2002; Deedwania et al, 2007a; Derosa et al, 2009; Erdine et al, 2009; Eriksson et al, 1998; Eriksson et al, 2011; Faergeman et al, 2008; Farnier et al, 2007; Farnier et al, 2008; Farnier et al, 2009; Feldman et al, 2004; Feldman et al, 2006; Ferdinand et al, 2006; Ferdinand et al, 2012; Flack et al, 2008; Florentin et al, 2011; Foody et al, 2010; Fox et al, 2007a; Fox et al, 2007b; Gagné et al, 2002; Gaudiani et al, 2005; Goldberg et al, 2004; Goldberg et al, 2006; Goldberg et al, 2009; Grimm et al, 2010; Gumprecht et al, 2011; Hall et al, 2009; Harley et al, 2007; Hing Ling et al, 2012; Hobbs et al, 2009; Hogue et al, 2008; Hunninghake et al, 2001; Illingworth et al,1994; Insull et al, 2007; Jones et al, 2003; Jones et al, 2009a; Jones et al, 2009b; Kerzner et al, 2003; Kipnes et al, 2010; Knapp et al, 2001; Koshiyama et al, 2008; Kumar et al, 2009; Lee et al, 2007; Leiter et al, 2007; Leiter et al, 2008; Lewis et al, 2007; Lloret et al, 2006; Marais et al, 2008; May et al, 2008; Mazza et al, 2008; Melani et al, 2003; Meredith et al, 2007; Messerli et al, 2006; Milionis et al, 2006; Mohiuddin et al, 2009; Motomura et al, 2009; Neutel et al, 2009; Nicholls et al, 2010; Ose et al, 2007; Ose et al, 2009; Ose et al, 2010; Park et al, 2005; Park et al, 2010; Pearson et al, 2007; Piorkowski et al, 2007; Polis et al, 2009; Preston et al, 2007; Reckless et al, 2008; Robinson et al, 2009; Rodenburg et al, 2007; Roeters van Lennep et al, 2008; Rogers et al, 2007; Rosenson et al, 2009; Rotella et al, 2010; Roth et al, 2010; Saito et al, 2002; Sansanayudh et al, 2010; Sasaki et al, 2008; Shafiq et al, 2007; Stalenhoef et al, 2005; Stein et al, 2003; Stein et al, 2004; Stein et al, 2007; Stein et al, 2008; Viigimaa et al, 2010; Vuorio et al, 2014; Winkler et al, 2007; Winkler et al, 2009; Wlodarczyk et al, 2008; Wolffenbuttel et al, 2005; Yoshitomi et al, 2006; Zieve et al, 2010).
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, and the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke (Afilalo et al, 2007; Afilalo et al, 2008; Ahmed et al, 2006; Amarenco et al, 2009a; Amarenco et al, 2009b; Asselbergs et al, 2004; Athyros et al, 2002; Athyros et al, 2007; Baigent et al, 2005; Barter et al, 2007; Briel et al, 2006; Bushnell et al, 2006; Byington et al; 1995; Cannon et al, 2004; Cannon et al, 2006; Cannon et al, 2015; Chan et al, 2010; Cholesterol Treatment Trialists' (CTT) Collaborators, 2008; Chonchol et al, 2007; Colhoun et al, 2004; Collins et al, 2003; Crouse et al, 2007; de Lemos et al, 2004; Deedwania et al, 2006; Deedwania et al, 2007b; Downs et al, 1998; Everett et al, 2010; Ford et al, 2007; Furberg et al, 1994; Hitman et al, 2007; Hulten et al, 2006; Khush et al, 2007; Knopp et al, 2006; Koenig et al, 2001; LaRosa et al, 2005; LaRosa et al, 2007; Liem et al, 2002; Meaney et al, 2009; Mood et al, 2007; Mora et al, 2010; Murphy et al, 2007; Nakamura et al, 2006; Neil et al, 2006; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; No authors listed, 1994; No authors listed, 2002; No authors listed, 2007; Olsson et al, 2007; O'Regan et al, 2008; Pedersen et al, 2005; Pitt et al, 1999; Pitt et al, 2012; Ray et al, 2005; Ray et al, 2006; Ridker et al, 2008; Ridker et al, 2009; Ridker et al, 2010; Rossebø et al, 2008; Sacks et al,1996; Sakamoto et al, 2007; Sato et al, 2008; Schmermund et al, 2006; Schoenhagen et al, 2006; Schouten et al, 2009; Schwartz et al, 2005; Scirica et al, 2006; Serruys et al, 2002; Sever et al, 2003; Sever et al, 2005; Shah et al, 2008; Shepherd et al, 1995; Shepherd et al, 2007; Shepherd et al, 2006; Shepherd J et al, 2002; Strandberg et al, 2009; Tavazzi L et al, 2008; Taylor et al, 2013; The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998; The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP), 1993; Thompson et al, 2004; Tikkanen et al, 2009; Waters et al, 2006; Wenger et al, 2007; Yu et al, 2007).
- Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events (Downs et al, 1998; Shepard et al, 1995).
- Specifically, the WOSCOPS trial (N=6,959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant 31% reduction in the risk of the combined endpoint of CHD death and nonfatal MI (P<0.001). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin (32%; P=0.033) (Shepard et al, 1995).

- The AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (P<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (Downs et al, 1998).
- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (P=0.0005) (Sever et al, 2003).
- Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (P=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (Colhoun et al, 2004; Sever et al, 2003; Sever et al, 2005).
- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02) (Ridker et al, 2008).
- Meta-analyses support the findings observed in the individual primary prevention trials (Baigent et al, 2005; CTT Collaborators et al, 2008; Mora et al, 2010; O'Regan et al, 2008; Taylor et al, 2011).
- The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs. 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; P=0.02), but the treatments were no different in terms of all-cause (P=0.81) or noncardiovascular (P=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (P<0.001) (Pedersen et al, 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; P=0.007) (Stoekenbroek et al, 2015).
- Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (P=0.02) (Byington et al, 1995; Chan et al, 2010; Crouse et al, 2007; Furberg et al, 1994; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; Schmermund et al, 2006; Schoenhagen et al, 2006).
- The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (Briel et al, 2006; Cannon et al, 2004; de Lemos et al, 2004; Liem et al, 2002).
- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (P=0.048) (Schwartz et al, 2005).
- Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on

improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization, and stroke by 16% compared to pravastatin (P=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (P=0.04) and unstable angina (P=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (P=0.11) (Cannon et al, 2004).

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation, however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (Wiggins et al, 2016).
- The 2016 scientific statement written by the American Heart Association (AHA) stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
    - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
    - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker amlodipine.
    - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
    - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (e.g. digoxin) (Wiggins et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single-Entity Agents				
atorvastatin	Tablet: 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 10 to 40 mg once daily; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day HeFH in pediatric patients 10 to 17	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day		
fluvastatin	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg	Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Extended-release tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily Extended-release tablet: 80 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly.	Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in two divided doses (immediate-release capsule). May be administered with or without food. Tablets may be taken at any time during the day (extended-release tablet). Tablets should be swallowed whole. (extended-release tablet).
lovastatin	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg	Hyperlipidemia: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day Prevention of CVD: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	Extended-release tablet should be taken at bedtime. Extended-release tablets should be swallowed whole. Immediate-release tablet should be taken with an evening meal.
pitavastatin	Tablet: 1 mg 2 mg 4 mg	Hyperlipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day	After initiation and/or upon titration, lipid levels should be	May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			analyzed after four weeks and dosage adjusted accordingly.	Tablets may be taken at any time during the day.
pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Prevention of CVD: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Pediatric patients: Ages eight to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.	May be administered with or without food. Tablets may be taken at any time during the day.
rosuvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg	Hyperlipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with HoFH: Tablet: initial, 20 mg once daily; Ages seven to 17 years: Tablet: 20 mg once daily Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged eight to less than 10 years: Tablet: maintenance, 5 to 10 mg/day Aged 10 to 17 years: Tablet: maintenance, 5 to 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosing in Asian patients: initial, 5 mg once daily Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/ ritonavir, lopinavir/ritonavir, or simeprevir.	May be administered with or without food. Tablets may be taken at any time during the day.
simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and	Tablets should be taken in the evening. Due to the increased risk of

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		lowering treatments or if such treatments are unavailable: Tablet: 40 mg once daily Prevention of CVD: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 10 to 17 years: Tablet: initial, 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	dosage adjusted accordingly. Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g. for 12 months or more) without evidence of muscle toxicity) while taking lomitapide. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when used with amiodarone, amlodipine, or ranolazine.	myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who have been taking the 80 mg dose chronically without evidence of muscle toxicity.
Combination Products				
amlodipine/ atorvastatin	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		amlodipine 10 mg daily and atorvastatin 80 mg daily. Patients requiring large LDL-C reductions (>45%) should initiate atorvastatin therapy at 40 mg once daily.	pressure goals. In general, wait seven to 14 days between titration steps. Titration may proceed more rapidly if clinically warranted, provided the patient is assessed frequently.	
ezetimibe/ atorvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Usual starting dose: 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/80 mg once daily. May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (> 55%). HoFH: 10/40 mg or 10/80 mg once daily.	After initiation or titration of doses, lipid levels may be analyzed after two or more weeks. For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenair alone or with ritonavir: Do not exceed 10/20 mg once daily. For patients taking nelfinavir: Do not exceed 10/40 mg once daily.	Tablets may be taken at any time of the day. May be administered with or without food.
ezetimibe/ simvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 or 10/20 mg once	After initiation and/or upon titration, lipid levels should be analyzed within two or more weeks and dosage adjusted accordingly. Decrease dose	May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy,

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		daily; maintenance, 10/10 to 10/40 mg/day	of VYTORIN by 50% if initiating lomitapide. VYTORIN dosage should not exceed 10/20 mg once day (or 10/40 mg once daily for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with amiodarone, amlodipine, or ranolazine.	particularly during the first year of treatment, use of the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.

*Pravachol 10 mg is no longer available, however, generic pravastatin 10 mg remains available.
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SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses of >20 mg have not been studied in this population.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum	Pregnancy Category X Unknown whether excreted in breast milk; not recommended.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	adult patients.	Safety and efficacy in children <10 years of age have not been established.		transaminases.	
fluvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 16 years of age for the treatment of HeFH. Safety and efficacy in children for other approved indications have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in severe renal dysfunction; doses above 40 mg per day have not been studied.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Potential excretion into breast milk; not recommended in breastfeeding women
lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin extended-release should not exceed 20 mg/day (ALTOPREV).	Approved for use in children 10 to 17 years of age for the treatment of HeFH (MEVACOR); maximum dose of 40 mg/day. Safety and efficacy in children <10 years of age have not been established (MEVACOR). Safety and efficacy in children have not been established (ALTOPREV).	Renal dosage adjustment is required; for creatinine clearances <30 mL/minute, use with caution and carefully consider doses >20 mg/day.	No dosage adjustment required.	Pregnancy Category X No data on excretion in breast milk; avoid breastfeeding when using this medication
pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established.	Renal dosage adjustment is required; for creatinine clearances 15 to 60 mL/ minute or end-stage renal disease	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			receiving hemodialysis, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended.		
pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children eight to 18 years of age for the treatment of HeFH. Safety and efficacy in children <8 years of age have not been established.	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast milk; contraindicated during breastfeeding.
rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children <7 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are recommended.	No dosage adjustment required in mild to moderate hepatic dysfunction. Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Limited data indicate that the drug is in breast milk; contraindicated during breastfeeding.
simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required for severe renal impairment: an	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; not recommended.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			initial dose of 5 mg/day with close monitoring is recommended.		
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Contraindicated in active liver disease.	Pregnancy Category X Unknown whether atorvastatin is excreted in breast milk; not recommended.
ezetimibe/ atorvastatin	The maximum dosage limit is 10/80 mg once daily for most patients.	Safety and efficacy have not been established.	No dosage adjustment is needed.	Contraindicated in patients with active hepatic disease or unexplained transaminase elevations.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients; prescribe with caution.	Safety and efficacy in children < 10 years old have not been established.	Use with caution doses exceeding 10/20 mg in patients with moderate to severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; not recommended.

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

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CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (CADUET [amlodipine/atorvastatin], ezetimbe/atorvastatin, and VYTORIN [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.

- Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.
- All products in this review are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.
- In 2004, the National Cholesterol Education Program (NCEP) published guidelines on the Implications of Recent Clinical Trials for the NCEP Adult Treatment Panel III, which stated the following:
    - When LDL-C lowering drug therapy is employed in high-risk or moderately-high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels.
    - Standard statin doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products such as bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols.
    - When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the statin dose may need to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
    - Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
    - In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.
    - For the treatment of HeFH, LDL-C lowering drugs should be initiated in young adulthood. Statins are considered first-line therapy Two-drug and sometimes three-drug therapy may be needed (Grundy et al, 2004).
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk reduction in adults (Stone et al, 2013).
    - These guidelines established four statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C >190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%
    - Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.
    - A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al, 2013).
    - Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.
- The 2015 AHA Scientific Statement on Familial Hypercholesterolemia (FH) recommends aggressive pharmacological treatment for patients with HeFH beginning at age eight to 10 years. Pharmacological treatment may also be considered in younger patients (less than eight years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after three months, then ezetimibe may be added. If LDL-C continues to be above goal after three months of two-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering

therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (Gidding et al, 2015).

- The 2016 United States Preventative Services Task Force (USPSTF) recommendations for preventive statin use for Primary Prevention of Cardiovascular Disease in Adults recommends the following:
    - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, hypertension, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
    - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of <10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a history of CVD when all of the following criteria are met: (1) they are aged 40 to 75 years (2) they have one or more CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
    - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥76 years without a history of MI or stroke (US Preventative Task Force, 2016).
- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.
- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.
- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase.
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.
- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

Table 5. Advantages and Disadvantages of Statins

Drug	Advantages	Disadvantages
Amlodipine	• Available generically as a single entity product and as a co-formulation with atorvastatin • Only antihypertensive that is co-formulated with a statin (atorvastatin)	• Associated with drug-drug interactions
Atorvastatin	• Available generically both alone and in combination with ezetimibe • Has been documented to have more potency in cholesterol-lowering than certain other statins • Cardiovascular outcomes studies support the use of the 80 mg strength in certain populations (e.g., as secondary	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

Drug	Advantages	Disadvantages
	prophylaxis following ST elevation MI)	
Ezetimibe	• Has been shown to be effective as an adjunctive lipid lowering agent when added to a statin • Co-formulated with simvastatin and atorvastatin in generic formulations	• Not considered as a first-line agent for the management of hyperlipidemia
Fluvastatin	• Available generically • Not associated with drug-drug interactions through the CYP3A4 isoenzyme system	• Associated with drug-drug interactions through the CYP2C9 isoenzyme system
Lovastatin	• Available generically	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Pitavastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	• Effect on cardiovascular morbidity and mortality has not been determined
Pravastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	
Rosuvastatin	• Available generically • Has been documented to have more potency in cholesterol-lowering than certain other statins	
Simvastatin	• Available generically both alone and in combination with ezetimibe	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

REFERENCES

- AbbVie Inc; withdrawal of approval of new drug applications for ADVICOR and SIMCOR. Federal Register website. Available at: https://www.federalregister.gov/articles/2016/04/18/2016-08894/abbvie-inc-withdrawal-of-approval-of-new-drug-applications-for-advicor-and-simcor. Updated on April 18, 2016. Accessed May 18, 2017.
- Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol. 2008;51(1):37-45.
- Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart. 2007;93(8):914-21.
- Ahmed S, Cannon CP, Murphy SA, et al. Acute coronary syndromes and diabetes: Is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. Eur Heart J. 2006;27(19):2323-9.
- Ai M, Otokozawa S, Asztalos BF, et al. Effects of maximal doses of atorvastatin vs rosuvastatin on small dense low-density lipoprotein cholesterol level. Am J Cardiol. 2008;101:315-8.
- ALTOPREV prescribing information. Covis Pharma. Zug, Switzerland. April 2016.
- Alvarez-Sala L, Cachofeiro V, Masana L, et al. Effects of fluvastatin extended-release (80 mg) alone and in combination with ezetimibe (10 mg) on low-density lipoprotein cholesterol and inflammatory parameters in patients with primary hypercholesterolemia: a 12-week, multicenter, randomized, open-label, parallel-group study. Clin Ther. 2008;30:84-97.
- Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009[a];40:1405-9.
- Amarenco P, Goldstein LB, Messig M, et al. Relative and cumulative effects of lipids and blood pressure control in Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. Stroke. 2009[b];40:2486-92.
- American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78-140.
- Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin vs fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism. 2007;56(11):1534-41.
- Asselbergs F, Diercks G, Hillege H, et al. Effects of fosinopril and pravastatin on cardiovascular events in patients with microalbuminuria. Circulation. 2004; Nov 2; 2809-16.
- Athyros VG, Mikhailidis DP, Liberopoulos EN, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant. 2007;22(1):118-27.

- Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal vs 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18(4):220-8.
- Avis HJ, Hutten BA, Gagne C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol. 2010;55(11):1121-6.
- Avis HJ, Vissers MN, Stein EA, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2007;27(8):1803-10.
- Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
- Ballantyne CM, Abate N, Yuan Z, et al. Dose-comparison study of the combination of ezetimibe and simvastatin (VYTORIN) vs atorvastatin in patients with hypercholesterolemia: the VYTORIN Vs Atorvastatin (VYVA) study. Am Heart J. 2005;149(3):464-73.
- Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006;151(5):975.e1-9.
- Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared to atorvastatin in adults with hypercholesterolemia. Am J Cardiol. 2004;93(12):1487-94.
- Ballantyne CM, Davidson MH, McKenny J, et al. Comparison of the safety and efficacy of a combination tablet of niacin extended-release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). Am J Cardiol. 2008;101:1428-36.
- Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003;107(19):2409-15.
- Ballantyne CM, Pitt B, Loscalzo J, et al. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). Am J Cardiol. 2013;111(4):506-9.
- Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol. 2007;99(5):673-80.
- Bardini G, Giorda CB, Pontiroli AE, et al. Ezetimibe+simvastatin vs doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol. 2010;9(20):1-8.
- Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007 Sep 27;357(13):1301-10.
- Bays H, Jones P, Mohiuddin S, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidology. 2008[a];2:426-35.
- Bays H, Sapre A, Taggart W, et al. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Curr Med Res Opin. 2008[b];24(10):2953-66.
- Bays HD, Averna, Majul C, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. Am J Cardiol. 2013;112(12):1885-95.
- Bays HE, Maki KC, McKenney J, et al. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin. 2010;26:907-15.
- Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004;26(11):1758-73.
- Becker DJ, Gordon RY, Morris PB, et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. Mayo Clin Proc. 2008;83(7):758-64.
- Betteridge DJ, Gibson JM. Effects of rosuvastatin on lipids, lipoproteins and apolipoproteins in the dyslipidaemia of diabetes. Diabet Med. 2007 [a];24(5):541-9.
- Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin vs atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). Am J Cardiol. 2007[b];100(8):1245-8.
- Braamskamp MJ, Langslet G, McCrindle BW, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study. J Clin Lipidol. 2015;9(6):741-50.
- Briel M, Schwartz GG, Thompson PL, de Lemos JA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA. 2006 May 3;295(17):2046-56.
- Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289-98.
- Bullano MF, Kamat S, Wertz DA, et al. Effectiveness of rosuvastatin vs atorvastatin in reducing lipid levels and achieving low-density-lipoprotein cholesterol goals in a usual care setting. Am J Health Syst Pharm. 2007;64(3):276-84.
- Bullano MF, Wertz DA, Yang GW, et al. Effect of rosuvastatin compared to other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. Pharmacotherapy. 2006;26(4):469-78.
- Bushnell CD, Griffin J, Newby LK, et al. Statin use and sex-specific stroke outcomes in patients with vascular disease. Stroke. 2006 Jun;37(6):1427-31.
- Byington RP, Furberg CD, Crouse JR, 3rd, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). Am J Cardiol. 1995; 76:54C-9C.
- CADUET prescribing information. Pfizer Inc. New York, NY. June 2017.
- Calza L, Manfredi R, Colangeli V, et al. Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolemia in HIV-infected patients receiving protease inhibitors (abstract). Curr HIV Res. 2008;6(6):572-8.
- Cannon C, Braunwald E, McCabe C, et al. Intensive vs moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350;15;1495-504.

- Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive vs moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
- Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387-97.
- Catapano AL, Davidson MH, Ballantyne CM, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet vs rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin. 2006;22(10):2041-53.
- Chan KL, Teo K, Dumesnil JG, et al; ASTRONOMERS Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTONOMER) trial. Circulation. 2010;121:306-14.
- Charland SL, Malone DC. Prediction of cardiovascular event risk reduction from lipid changes associated with high potency dyslipidemia therapy. Curr Med Res Opin. 2010 Feb;26(2):365-75.
- Chenot F, Montant PF, Marcovitch O, et al. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest. 2007 May;37(5):357-63.
- Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12;371(9607):117-25.
- Chonchol M, Cook T, Kjekshus J, et al. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis. 2007 Mar;49(3):373-82.
- Clearfield MB, Amerena J, Bassand JP, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia-Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006 Dec 21;7:35.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc., www.clinicalpharmacology.com. Accessed May 18, 2017.
- Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.
- Coll B, Aragones G, Parra S, et al. Ezetimibe effectively decreases LDL-cholesterol in HIV-infection patients. AIDS. 2006 Aug;20(12):1675-7.
- Collins R, Armitage J, Parish S, et al; Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003;361:2005-16.
- Conard SE, Bays HE, Leiter LA, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) vs uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol 2008;102:1489-94.
- Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
- CRESTOR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington (DE). May 2016.
- Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007 Mar 28; 297(12):1344-53.
- Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002 Dec 18;40(12):2125-34.
- de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16.
- Deedwania P, Barter P, Carmena R, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28.
- Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive vs moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007[b] Feb 13;115(6):700-7.
- Deedwania PC, Gupta M, Stein M, et al. Comparison of rosuvastatin vs atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). Am J Cardiol. 2007[a] Jun 1;99(11):1538-43.
- Derosa G, Maffioli P, Salvadeo SA, et al. Fenofibrate, simvastatin and their combination in the management of dyslipidaemia in type 2 diabetic patients. Curr Med Res Opin. 2009;25:1973-83.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA. 1998;279(20):1615-22.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 18, 2017.
- Erdine S, Ro YM, Tse HF, et al. Single-pill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study). J Human Hypertens. 2009;23:196-210.
- Eriksson M, Budinski D, Hounslow N. Comparative efficacy of pitavastatin and simvastatin in high-risk patients: a randomized controlled trial. Adv Ther. 2011 Sep;28(9):811-23.
- Eriksson M, Hådell K, Holme I, et al. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med. 1998 May;243(5):373-80.
- Everett BM, Glynn RJ, MacFadyen JG, et al. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation. 2010;121:143-50.
- Faergeman O, Hill L, Windler E, et al. Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia: results from the ECLIPSE study. Cardiology. 2008;111:219-28.
- Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared to rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – the IN-CROSS study. Int J Clin Pract. 2009;63:534-5.
- Farnier M, Perevozskaya I, Taggart WV, et al. VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate. J Lipid Res. 2008;49:2641-7.
- Farnier M, Roth E, Gil-Extremera B, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J. 2007 Feb;153(2):335.e1-8.

- Feldman T, Davidson M, Shah A, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older vs younger patients with primary hypercholesterolemia: a post Hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
- Feldman T, Koren M, Insull W Jr, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration vs simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004 Jun 15;93(12):1481-6.
- Ferdinand KC, Clark LT, Watson KE, et al. Comparison of efficacy and safety of rosuvastatin vs atorvastatin in African-American patients in a six-week trial. Am J Cardiol. 2006 Jan 15;97(2):229-35.
- Ferdinand KC, Davidson MH, Kelly MT, et al. One-year efficacy and safety of rosuvastatin + fenofibric acid combination therapy in patients with mixed dyslipidemia. Evaluation of dose response. Am J Cardiovasc Drugs. 2012;12(2):117-25.
- Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. Mayo Clin Proc. 2008 Jan;83(1):35-45.
- Florentin M, Liberopoulos EN, Moutzouri E, et al. The effect of simvastatin alone vs simvastatin plus ezetimibe on the concentration of small density low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Curr Med Res Opin. 2011;27(3):685-92.
- Foody JM, Brown WV, Zieve F, et al. Safety and efficacy of ezetimibe/simvastatin combination vs atorvastatin alone in adults ≥65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD Study). Am J Cardiol. 2010;106:1255-63.
- Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007 Oct 11;357(15):1477-86.
- Fox KM, Gandhi SK, Ohsfeldt RL, et al. Effectiveness of rosuvastatin in low-density lipoprotein cholesterol lowering and National Cholesterol Education Program Adult Treatment Panel guideline III LDL-C goal attainment compared to other statins among diabetes mellitus patients: a retrospective study using an electronic medical records dataset in the United States. Curr Med Res Opin. 2007[a];23(9):2125-33.
- Fox KM, Gandhi SK, Ohsfeldt RL, et al. Comparison of low-density lipoprotein cholesterol reduction after switching patients on other statins to rosuvastatin or simvastatin in a real-world clinical practice setting. Am J Manag Care. 2007 [b];13(Suppl 10):S270-5.
- Furberg CD, Adams HP, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic carotid artery progression study (ACAPS) research group. Circulation. 1994 Oct; 90(4):1679-87.
- Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002 May 28;105(21):2469-75.
- Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes Obes Metab. 2005 Jan;7(1):88-97.
- Gidding SS, Ann Champagne M, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015 Dec 1;132(22):2167-92.
- Goldberg AC, Bays HE, Ballantyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol. 2009;103:515-22.
- Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 May;79(5):620-9.
- Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
- Grimm R, Malik M, Yunis C, et al; TOGETHER Investigators. Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial. Vasc Health Risk Manag. 2010;6:261-71.
- Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
- Gumprecht J, Gosho M, Budinski D, et al. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes Obes Metab. 2011 Nov;13(11):1047-55.
- Hall AS, Jackson BM, Farrin AJ, et al. A randomized, controlled trial of simvastatin vs rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial (abstract). Eur J Cardiovasc Prev Rehabil. 2009 Dec;16(6):712-21.
- Harley CR, Gandhi SK, Anoka N, et al. Understanding practice patterns and low-density lipoprotein cholesterol goal attainment implications of switching patients from simvastatin in a health plan setting. Am J Manag Care. 2007 Dec;13 Suppl 10:S276-81.
- Hing Ling PK, Civeira F, Dan AG, et al. Ezetimibe/simvastatin 10/40 mg vs atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis. 2012 Jan 31;11:18.
- Hitman GA, Colhoun H, Newman C, et al. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabet Med. 2007 Dec;24(12):1313-21.
- Hobbs R, Gensini G, Mancini J, et al. International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme (abstract). Eur J Cardiovasc Prev Rehabil. 2009 Aug;16(4):472-80.
- Hogue JC, Lamarche B, Tremblay AJ, et al. Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism. 2008;57:380-6.
- Hulten E, Jackson JL, Douglas K, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Sep 25;166(17):1814-21.
- Hunninghake D, Insull W Jr, Toth P, et al. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis. 2001 Oct;158(2):407-16.
- Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. Arch Intern Med. 1994;154:1586-95.
- Insull W Jr, Ghali JK, Hassman DR, et al. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. Mayo Clin Proc. 2007 May;82(5):543-50.

- Jones P, Davidson M, Goldberg A, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidology. 2009[a];3:125-37.
- Jones P, Davidson M, Kashyap M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. Atherosclerosis. 2009[b];204:208-215.
- Jones P, Davidson M, Stein E, et al. Comparison of the efficacy and safety of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92:152-60.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45:2160-236.
- Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol. 2003 Feb 15;91(4):418-24.
- Khush KK, Waters DD, Bittner V, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation. 2007 Feb 6;115(5):576-83.
- Kipnes MS, Roth EM, Rhyme JM, et al. Year two assessment of fenofibric acid and moderate-dose statin combination. A Phase 3, open-label, extension study. Clin Drug Investig. 2010;30(10):51-61.
- Knapp HH, Schrott H, Ma P, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med. 2001 Apr;110(5):352-60.
- Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular endpoints in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006 Jul;29(7):1478-85.
- Koenig W, Ridker PM. Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation risk ≥5% or Framingham risk >20%: post hoc analyses of the JUPITER trial requested by European health authorities. Eur Heart J. 2001;32:75-83.
- Koshiyama H, Taniguchi A, Tanaka K, et al. Effects of pitavastatin on lipid profiles and high-sensitivity CRP in Japanese subjects with hypercholesterolemia: Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN) investigators. J Atheroscler Thromb. 2008;15:345:50.
- Kumar SS, Lahey KA, Day A, et al. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate vs atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis. 2009;8(56):1-8.
- LaRosa JC, Grundy SM, Kastelein JJ, et al. Treating to New Targets (TNT) Steering Committee and Investigators. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). Am J Cardiol. 2007 Sep 1;100(5):747-52.
- LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005 Apr 7;352(14):1425-35.
- Lee SH, Chung N, Kwan J, et al. Comparison of the efficacy and tolerability of pitavastatin and atorvastatin: an 8-week, multicenter, randomized, open-label, dose-titration study in Korean patients with hypercholesterolemia. Clin Ther. 2007;29(11):2365-73.
- Leiter LA, Bays H, Conard S, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared to uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008;102:1495-501.
- Leiter LA, Rosenson RS, Stein E, et al. Efficacy and safety of rosuvastatin 40 mg vs atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study. Atherosclerosis. 2007 Oct;194(2):e154-64.
- LESCOL and LESCOL XL prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. October 2012.
- Lewis JH, Mortensen ME, Zweig S, et al. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 2007 Nov;46(5):1453-63.
- Liem AH, van Boven AJ, Veeger NJ, et al. Effects of fluvastatin on ischemia following acute myocardial infarction: a randomized trial. Eur Heart J. 2002;23:1931-7.
- LIPITOR prescribing information. Pfizer, Inc. New York, NY. June 2017.
- LIVALO prescribing information. Kowa Pharmaceuticals America, Inc. Montgomery, AL: December 2016.
- Lloret R, Ycas J, Stein M, et al; STARSHIP Study Group. Comparison of rosuvastatin vs atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial). Am J Cardiol. 2006 Sep 15;98(6):768-73.
- Marais AD, Raal FJ, Stein EA, et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008 Mar;197(1):400-6.
- May HT, Anderson JL, Pearson RR, et al. Comparison of effects of simvastatin alone vs fenofibrate alone vs simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol. 2008;101:486-9.
- Mazza F, Stefanutti C, Di Giacomo S, et al. Effects of low-dose atorvastatin and rosuvastatin on plasma lipid profiles: a long-term, randomized, open-label study in patients with primary hypercholesterolemia. Am J Cardiovasc Drugs. 2008;8:265-70.
- Meaney A, Ceballos G, Asbun J, et al. The VYTORIN on Carotid intima-media Thickness and Overall arterial Rigidity study (VYCTOR). J Clin Pharmacol. 2009;49:838-847.
- Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J. 2003 Apr;24(8):717-28.
- Meredith KG, Horne BD, Pearson RR, et al. Comparison of effects of high (80 mg) vs low (20 mg) dose of simvastatin on C-reactive protein and lipoproteins in patients with angiographic evidence of coronary arterial narrowing. Am J Cardiol. 2007 Jan 15;99(2):149-53.
- Messerli FH, Bakris GL, Ferrera D, et al. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. J Clin Hypertens (Greenwich). 2006 Aug;8(8):571-81.
- MEVACOR prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. February 2014.
- Milionis HJ, Rizos E, Kostapanos M, et al. Treating to target patients with primary hyperlipidemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin. 2006 Jun;22(6):1123-31.
- Mohiuddin S, Pepine C, Kelly M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J. 2009;157:195-203.

- Mood GR, Bavry AA, Roukoz H, et al. Meta-analysis of the role of statin therapy in reducing myocardial infarction following elective percutaneous coronary intervention. Am J Cardiol. 2007 Sep 15;100(6):919-23.
- Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010;121:1069-77.
- Motomura T, Okamoto M, Kitamura T, et al. Effects of pitavastatin on serum lipids and high sensitivity c-reactive protein in Type 2 diabetic patients. J Atheroscler Thromb. 2009;16:546-52.
- Murphy SA, Cannon CP, Wiviott SD, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to ZOCOR and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol. 2007 Oct 1;100(7):1047-51.
- Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled study. Lancet. 2006;368:1155-63.
- Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.
- Neutel JM, Bestermann WH, Dyess EM, et al. The use of a single-pill calcium channel blocker/statin combination in the management of hypertension and dyslipidemia: a randomized, placebo-controlled, multicenter study. J Clin Hypertens (Greenwich). 2009;11:22-30.
- Nicholls S, Brandrup-Wognsen G, Palmer M, et al. Meta-analysis of comparative efficacy of increasing dose of atorvastatin vs rosuvastatin vs simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol. 2010;105:69-76.
- Nicholls SJ, Tuzcu EM, Sipahi I, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11):1553-7.
- Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006 Apr 5;295(13):1556-65.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared to moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial (REVERSAL). JAMA. 2004 Mar 3;291(9):1071-80.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005 Jan 6;352(1):29-38.
- No authors listed. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 356 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
- No authors listed. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet. 1994;344:1383-9.
- No authors listed. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007 Apr;45(4):645-54.
- Olsson AG, Schwartz GG, Szarek M, et al. Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). Am J Cardiol. 2007 Mar 1;99(5):632-5.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 18, 2017.
- O'Regan C, Wu P, Arora P, et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med. 2008 Jan;121(1):24-33.
- Ose L, Budinski D, Hounslow N, et al. Comparison of pitavastatin with simvastatin in primary hypercholesterolemia or combined dyslipidemia. Curr Med Res Opin. 2009;25(11):2755-64.
- Ose L, Budinski D, Hounslow N, et al. Long-term treatment with pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia. Atherosclerosis. 2010;210:202-8.
- Ose L, Johnson-Levonas A, Reyes R, Lin J, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
- Park A, Kang HJ, Rim SJ, et al. A randomized, open-label study to evaluate the efficacy and safety of pitavastatin compared to simvastatin in Korean patients with hypercholesterolemia. Clin Ther. 2005;27(7):1074-82.
- Park JS, Kim YJ, Choi JY, et al. Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Korean J Intern Med. 2010;25:27-35.
- Pearson T, Ballantyne C, Sisk C, et al. Comparison of effects of ezetimibe/simvastatin vs simvastatin vs atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
- Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45.
- Piorkowski M, Fischer S, Stellbaum C, et al. Treatment with ezetimibe plus low-dose atorvastatin compared to higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol. 2007 Mar 13;49(10):1035-42.
- Pitt B, Loscalzo J, Monyak J, et al. Comparison of lipid-modifying efficacy of rosuvastatin vs atorvastatin in patients with acute coronary syndrome (from the LUNAR study). Am J Cardiol. 2012 May 1;109(9):1239-46.
- Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared to angioplasty in stable coronary artery disease. Atorvastatin vs Revascularization Treatment Investigators. N Engl J Med. 1999 Jul 8;341(2):70-6.
- Polis AB, Abate N, Catapano AL, et al. Low-density lipoprotein cholesterol reduction and goal achievement with ezetimibe/simvastatin vs atorvastatin or rosuvastatin in patients with diabetes, metabolic syndrome, or neither disease, stratified by national cholesterol education program risk category. Metab Syndr Relat Disord. 2009;7(6):601-10.
- PRAVACHOL prescribing information. Bristol-Myers Squibb. Princeton, NJ. June 2017.
- Preston RA, Harvey P, Herfert O, et al. A randomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: the respond trial. J Clin Pharmacol. 2007 Dec;47(12):1555-69.

- Ray KK, Bach RG, Cannon CP, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. Eur Heart J. 2006 Oct;27(19):2310-6.
- Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2005 Oct 18;46(8):1405-10.
- Reckless J, Henry P, Pomykaj T, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the statin dose in patients admitted to the hospital for a recent coronary event (INFORCE). Int J Clin Pract. 2008;62:539-554.
- Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-207.
- Ridker PM, MacFadyen J, Cressman M, et al. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein. J Am Coll Cardiol. 2010;55(12):1266-73.
- Ridker PM, MacFadyen JG, Fonseca FAH, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low-density lipoprotein cholesterol and elevated high-sensitivity c-reactive protein. Circ Cardiovasc Qual Outcomes. 2009;2:616-23.
- Robinson JG, Ballantyne CM, Grundy SM, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin vs atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (VYMET). Am J Cardiol. 2009;103:1694-702.
- Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. Circulation. 2007 Aug 7;116(6):664-8.
- Roeters van Lennep H, Liem A, et al. The efficacy of statin monotherapy up-titration vs switching to ezetimibe/simvastatin (EASEGO). Curr Med Res Opin. 2008;24:685-694.
- Rogers SL, Magliano DJ, Levison DB, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. Clin Ther. 2007 Feb;29(2):242-52.
- Rosenson RS, Otvos JD, Hsia J, et al. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. Diabetes Care. 2009;32:1087-91.
- Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (SEAS). N Engl J Med. 2008;359:1343-56.
- Rotella CM, Zaninelli A, Le Grazie C, et al. Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes. Lipids Health Dis. 2010;9(80):1-8.
- Roth EM, Rosenson RS, Carlson DM, et al. Efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg in patients with mixed dyslipidemia-a phase 3 study. Cardiovasc Drugs Ther. 2010;24:421-8.
- Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. The Cholesterol and Recurrent Events Trial (CARE). N Engl J Med.1996 Oct; 335(14):1001-9.
- Saito Y, Yamada N, Teramoto T, et al. A randomized, double-blind trial comparing the efficacy and safety of pitavastatin vs pravastatin in patients with primary hypercholesterolemia. Atherosclerosis. 2002;162:373-9.
- Sakamoto T, Kojima S, Ogawa H, et al. Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI. Circ J. 2007 Sep;71(9):1348-53.
- Sansanayudh N, Wongwiwatthananukit S, Putwai P, et al. Comparative efficacy and safety of low-dose pitavastatin vs atorvastatin in patients with hypercholesterolemia. Ann Pharmacother. 2010;44:415-23.
- Sasaki J, Ikeda Y, Kuribayashi T, et al. A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. Clin Ther. 2008;30(6):1089-100.
- Sato H, Kinjo K, Ito H, et al. Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study. Circ J. 2008;72:17-22.
- Schmermund A, Achenbach S, Budde T, et al. Effect of intensive vs standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006 Jan 24;113(3):427-37.
- Schoenhagen P, Tuzcu EM, Apperson-Hansen C, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation. 2006 Jun 20;113(24):2826-34.
- Schouten O, Boersma E, Hoeks S, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med. 2009;361:980-989.
- Schwartz GG, Olsson AG, Szarek M, et al. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. Diabetes Care. 2005 Oct;28(10):2508-13.
- Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2006 Jun 6;47(11):2326-31.
- Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. LESCOL Intervention Prevention Study (LIPS). JAMA. 2002;287(24):3215-22.
- Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58.
- Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care. 2005 May;28(5):1151-7.
- Shafiq N, Bhasin B, Pattanaik S, et al. A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia. Int J Clin Pharmacol Ther. 2007 Oct; 45(10):548-55.
- Shah SJ, Waters DD, Barter P, et al. Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery. J Am Coll Cardiol. 2008;51:1938-43.
- Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006 Jun;29(6):1220-6.

- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet. 2002;360:1623-30.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. The West of Scotland Coronary Prevention Study (WOSCOPS). NEJM. 1995;333(20):1301-7.
- Shepherd J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003 Mar 6;91(5A):11C-7C.
- Shepherd J, Kastelein JJ, Bittner V, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol. 2007 Nov;2(6):1131-9.
- Stalenhoef A, Ballantyne C, Sarti C, et al. A comparative study with rosuvastatin in subjects with metabolic syndrome: Results of The Comets Study. Eur Heart J. 2005;1093:822-9.
- Stein E, Ballantyne C, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol. 2008;101:490-496.
- Stein E, Stender S, Mata P, Sager P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;447-55.
- Stein EA, Amerena J, Ballantyne CM, et al. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. Am J Cardiol. 2007 Nov 1;100(9):1387-96.
- Stein EA, Strutt K, Southworth H, et al. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. Am J Cardiol. 2003 Dec 1;92(11):1287-93.
- Stoekenbroek RM, Boekholdt SM, Fayyad R, et al. High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease. Heart. 2015;101:356-62.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in Adults: A report of the American College of Cardiology/American Heart Association. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.
- Strandberg TE, Holme I, Faergeman O, et al. Comparative effect of atorvastatin (80 mg) vs simvastatin (20 to 40 mg) in preventing hospitalizations for heart failure in patients with previous myocardial infarction. Am J Cardiol. 2009;103:1381-5.
- Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1231-9.
- Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2013, Jan 31;(1):CD004816. doi: 10.1002/14651858.CD004816.pub5.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.
- The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339(19):1349-57.
- The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP). Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dL) plus two additional atherosclerotic risk factors. Am J Cardiol. 1993;72:1031-7.
- Thompson P, Meredith I, Anerena J, et al. Effect of pravastatin compared to placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: The Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J. 2004 Jul;148(1):e2.
- Tikkanen MJ, Holme I, Cater NB, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 vs ≥65 years with coronary heart disease (from the Incremental Decrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol. 2009;103:577-82.
- US Preventive Services Task Force. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;316(19):1997-2007. *Circulation*. 2016;134:e468-e495.
- Viigimaa M, Vaverkova H, Farnier M, et al. Ezetimibe/simvastatin 10/20 mg vs rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids Health Dis. 2010 Nov 4;9:127.
- Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews. 2014, Issue 7. Art. No.:CD006401. DOI: 10.1002/14651858.CD006401.pub3.
- VYTORIN prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. October 2016.
- Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol. 2006 Nov 7;48(9):1793-9.
- Wenger NK, Lewis SJ, Herrington DM, et al; Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Intern Med. 2007 Jul;147(1):1-9.
- Wiggins B, Saseen J, Page R, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134:e468-e495.
- Winkler K, Ablethauser CB, Gimpelewicz C, et al. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. Clin Ther. 2007;29:1987-2000.
- Winkler K, Schewe T, Putz G, et al. Fluvastatin/fenofibrate vs simvastatin/ezetimibe in patients with metabolic syndrome: different effects on LDL-profiles. Eur J Clin Invest. 2009;39(6):463-70.
- Wlodarczyk J, Sullivan D, Smith M. Comparison of benefit and risks of rosuvastatin vs atorvastatin for a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008;102:1654-62.
- Wolffenbuttel BH, Franken AA, Vincent HH. Cholesterol-lowering effects of rosuvastatin compared to atorvastatin in patients with type 2 diabetes: the CORALL study. J Intern Med. 2005 Jun;257(6):531-9.
- Wongwiwatthananukit S, Sansanayudh N, Dhummauppakorn R, et al . Efficacy and safety of rosuvastatin every other day compared to once daily in patients with hypercholesterolemia. Ann Pharmacother. 2006 Nov;40(11):1917-23.
- Yoshitomi Y, Ishii T, Kaneki M, et al. Efficacy of a low dose of pitavastatin compared to atorvastatin in primary hyperlipidemia: results of a 12-week, open label study. J Atheroscler Thromb. 2006;13(2):108-13.

- Yu CM, Zhang Q, Lam L, et al. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intima-medial thickness in patients with coronary heart disease. Heart. 2007 Aug;93(8):933-9.
- Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and efficacy of ezetimibe added to atorvastatin vs up titration of atorvastatin to 40 mg in patients >or = 65 years of age (ZETELD). Am J Cardiol. 2010;105:656-63.
- ZOCOR prescribing information. Merck & Co, Inc. Whitehouse Station, NJ. March 2015.

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Therapeutic Class Overview
Antipsoriatic Agents

INTRODUCTION

- The goal of treatment for patients with psoriasis is to induce and maintain remission. There are three main treatment modalities available at present for the treatment of psoriasis: topical agents, phototherapy, and systemic agents. According to the American Academy of Dermatology (AAD), for the treatment of psoriasis, topical preparations alone or in combination with phototherapy are recommended before using biologic or systemic therapy. Topical therapies are the mainstay for mild disease either as monotherapy or in combination, and topical therapies are also commonly used in conjunction with phototherapy, traditional systemic agents, or biologic agents for moderate to severe disease. Phototherapy, photochemotherapy, and traditional systemic agents are generally used for moderate or severe disease and in situations in which topical therapy is ineffective or otherwise contraindicated (Menter et al, 2011; Usatine et al, 2013).
- Topical corticosteroids (e.g., betamethasone, clobetasol, triamcinolone, etc.) are the cornerstone of treatment for the majority of patients with psoriasis. Their effectiveness in treating psoriasis is due to anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (Menter et al, 2011). Due to these side effects, several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- Other topical antipsoriatic agents include anthralin, calcitriol, calcipotriene, and tazarotene. These agents are available in a variety of vehicles. Early forms of treatment also included coal tar. In the United States, coal tar use has declined due to lack of standardization of available compounds and the development of other agents with less cosmetic issues such as odor and staining.
- Oral antipsoriatic systemic agents are typically reserved for moderate to severe psoriasis and are often combined with other therapies. Acitretin, a topical retinoid, modulates the cellular differentiation of the epidermis and is known to have immunomodulatory and anti-inflammatory activity (Menter et al, 2009[b]). Acitretin is most effective as a maintenance therapy, usually after the disease has been stabilized, or in combination with other treatments such as phototherapy (Villasenor-Park et al, 2012). Methoxsalen is a naturally occurring photosensitivity agent (psoralen) that enhances skin reactivity to ultraviolet light A (UVA). The combination of psoralen and UVA is referred to as photochemotherapy or PUVA. PUVA is an option for psoriasis that does not respond to topical medications alone or for lesions that are too extensive for topical treatment (Menter et al, 2010).
- Agents included in this review are the topical and oral antipsoriatics, which are listed in Table 1. Biologics (i.e., adalimumab, adalimumab-atto, etanercept, etanercept-szzs, infliximab, infliximab-dyyb, ixekizumab, secukinumab, and ustekinumab) that are used to treat psoriasis and other inflammatory/immunologic diseases are not included in this review. Topical corticosteroids are also not included in this review.
- Medispan Class: Antipsoriatics, Antipsoriatic – Systemic, and Topical Steroid Combinations

Table 1. Medications Included Within Class Review

Generic	Brand	Manufacturer	FDA Approval Date	Generic Availability
Topical Agents				
Anthralin	DRITHOCREME® HP cream	Summers	-*	-
	ZITHRANOL-RR® cream	Elorac	-*	-
	ZITHRANOL® shampoo	Elorac	-*	-
Calcipotriene	DOVONEX® cream	Leo Pharma	07/22/1996	✔
	SORILUX® foam	Stiefel	10/06/2010	-
	Topical ointment	Glenmark Generics	03/24/2010	✔
	Topical scalp solution	various	03/03/1997	✔
Calcitriol	VECTICAL® ointment	Galderma	01/23/2009	-
Tazarotene	TAZORAC® cream	Allergan	09/29/2000	-
	TAZORAC® gel		06/13/1997	-
Calcipotriene/ Betamethasone dipropionate	ENSTILAR® foam	Leo Pharm	10/16/2015	-
	TACLONEX® suspension		05/09/2008	-
	TACLONEX® ointment		01/09/2006	✔
Oral Systemic Agents				
Acitretin	SORIATANE® capsules	Stiefel	10/28/1996	✔
Methoxsalen**	OXSORALEN-ULTRA® capsules	Valeant	10/30/1986	✔

*Anthralin products are unapproved marketed drugs that have not been formally evaluated by the Food and Drug Administration (FDA) as it was initially marketed before the Federal, Food, Drug, and Cosmetic Act was passed.
**8-MOP® capsules are still listed in the FDA Orange Book but are no longer marketed according to a phone conversation with the manufacturer in March 2017.
(DRUGS@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug(s)	Psoriasis (Quiescent or Chronic)	Severe Psoriasis	Plaque Psoriasis	Photo-chemotherapy	Acne Vulgaris
Topical Agents					
Anthralin (DRITHROCREME, ZITHRANOL-RR, ZITHRANOL)	✔				
Calcipotriene (DOVONEX, SORILUX, Calcipotriene ointment)			✔ *		
Calcitriol (VECTICAL)			✔ **		
Tazarotene (TAZORAC)			✔		✔ †
Calcipotriene/ betamethasone dipropionate (ENSTILAR foam)			✔		
Calcipotriene/ betamethasone dipropionate (TACLONEX suspension)			✔ ‡		
Calcipotriene/ betamethasone dipropionate (TACLONEX ointment)			✔ ‖		

Drug(s)	Psoriasis (Quiescent or Chronic)	Severe Psoriasis	Plaque Psoriasis	Photo-chemotherapy	Acne Vulgaris
Oral Systemic Agents					
Acitretin (SORIATANE)		✔			
Methoxsalen (OXSORALEN-ULTRA)				✔ ¥	

*****SORILUX indicated for plaque psoriasis of scalp and body in patients 18 years or older; Calcipotriene Topical Solution, 0.005% (Scalp Solution) is indicated for the treatment of chronic, moderately severe psoriasis of the scalp.
******Mild to moderate plaque psoriasis in adults 18 years and older.
†TAZORAC 0.1% cream and gel
‡TACLONEX suspension indicated for plaque psoriasis of the scalp and body in patients 18 years and older. Additionally, the suspension is indicated for plaque psoriasis of the scalp in patients ages 12 to 17 years.
‖TACLONEX ointment is indicated for plaque psoriasis in patients 12 years of age and older. Limitations of use: Do no use on face, axillae or groin and do not use if skin atrophy is present at the treatment site.
¥For control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.

(Prescribing Information: Calcipotriene ointment, 2015; Calcipotriene solution, 2015; DRITHOCREME, 2014; ENSTILAR, 2016; DOVONEX, 2015; OXSORALEN-ULTRA, 2015; SORIATANE, 2015; SORILUX, 2013; TACLONEX ointment, 2017; TACLONEX suspension, 2017; TAZORAC cream, 2013; TAZORAC gel, 2014; VECTICAL, 2012; ZITHRANOL-RR, 2008; ZITHRANOL shampoo, 2011)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Various strengths and formulations of anthralin or dithranol have been evaluated (Fredriksson, 1983; Jones et al, 1985). Results from these trials support efficacy of anthralin in the treatment of psoriasis with no significant differences identified between dosage strength, formulation, or administration.
- Topical calcipotriene has demonstrated favorable efficacy in treating psoriasis in several studies with marked improvements in clearing of psoriatic lesions occurring in approximately 50 to 70% of patients (Highton et al 1995; Dubertret et al, 1992; Thaci et al, 2001). Treatment success was reported in patients with psoriasis who were treated with topical calcipotriene foam in two eight-week, multicenter, randomized, double-blind, vehicle-controlled clinical trials (Feldman et al, 2012; Feldman et al, 2013).
- For the treatment of plaque psoriasis, topical calcipotriene has demonstrated favorable efficacy when combined with betamethasone, psoralen plus ultraviolet A (PUVA), and methotrexate (Buckley et al, 2008; De Jong et al, 2003; Kragballe et al, 2009; Luger et al, 2008; Ortonnne et al, 2009; Ozkan et al, 2012; Torras et al, 2014; van de Kerkhof et al, 2009). The combination of calcipotriene plus betamethasone has demonstrated superior efficacy when compared to monotherapy with either calcipotriene or betamethasone or placebo in several clinical trials (Buckley et al, 2008; Douglas et al, 2002; Guenther et al, 2002; Jemec et al, 2008; Kaufman et al, 2002; Kragballe et al, 2004; Kragballe et al, 2009; Luger et al, 2008; Ortonne et al, 2009; Papp et al, 2003; Parslew et al, 2005; Singh et al, 2000; van de Kerkhof et al, 2005; van de Kerkhof et al, 2009; van de Kerkhoff et al, 2004).
- The efficacy of calcitriol ointment for the treatment of mild to moderate plaque psoriasis was demonstrated in two double-blind, randomized controlled studies involving 839 patients. Calcitriol applied twice daily for eight weeks was significantly more effective than the vehicle. Additionally, there were no clinically relevant changes in calcium homeostasis or other routine laboratory parameters in calcitriol-treated patients (Lebwohl et al, 2007).
- Head-to-head trials comparing the vitamin D analogues have been conducted. Ortonne et al found calcitriol to be significantly better tolerated than calcipotriol in sensitive skin fold areas (Ortonne et al, 2003). In another 12-week, randomized trial in patients with chronic plaque psoriasis, calcitriol demonstrated similar efficacy to calcipotriol and had a significantly better safety profile (Zhu et al, 2007).
- Head-to-head trials comparing therapies from different medication classes for the treatment of psoriasis also exist. Veronikis et al compared calcipotriene to coal tar and found that both agents were effective in the treatment of plaque psoriasis with no significant differences found between treatment groups (P value not reported) (Veronikis et al, 1999). Calcipotriol solution has been compared to clobetasol shampoo, with clobetasol being found to be significantly more efficacious in terms of total severity score measures as well as global severity score (P<0.05 for all) (Reygagne, 2005).

- Tazarotene was shown to be more effective than placebo in treating plaque psoriasis (Weinstein et al, 1997). Results demonstrated that both tazarotene 0.1% and 0.5% gel were significantly more effective than placebo in reducing the severity of signs and symptoms of target lesions (P<0.05). A second, placebo-controlled trial with the same methodology found similar results (Weinstein et al, 2003). Topical tazarotene in combination with a low-, mid-, and high-potency topical corticosteroid has been evaluated in patients with mild to moderate plaque psoriasis (Guenther et al, 2000; Lebwohl et al, 1998). While all treatments were effective, the tazarotene and topical corticosteroid combination produced significantly higher treatment success rates at weeks two, eight, and 12 vs tazarotene monotherapy (all P<0.05). Bowman et al compared the combination of tazarotene gel plus calcipotriene ointment to clobetasol ointment in patients with stable psoriasis and found that both treatments were effective in reducing scaling, plaque elevation, and overall lesion severity with no significant differences between the two groups (P=0.93, P=0.76, and P=0.29, respectively) (Bowman et al, 2002).
- Acitretin has been shown to be effective in the treatment of patients with moderate to severe psoriasis in open-label studies and controlled clinical trials (Olsen et al, 1989; Tosti et al, 2009). In combination with calcipotriol, acitretin demonstrated improved clinical outcomes compared to acitretin alone or placebo (Rim et al, 2003; van de Kerkhof et al, 1998). Acitretin in combination with phototherapy can enhance treatment efficacy for patients with moderate to severe chronic plaque psoriasis that does not clear using UVB, PUVA, or acitretin alone. Compared with acitretin or UV light monotherapy, the combination regimen enhances efficacy and limits treatment frequency, duration, and cumulative doses (Lebwohl et al, 2001).
- Several large multicenter trials have demonstrated the efficacy of oral methoxsalen with UVA (PUVA) in psoriasis, indicating clearance of lesions in 70% to 89% of patients (Henseler et al, 1981; Roenigk et al, 1979; Melski et al, 1977). Two systematic reviews of the large majority of PUVA studies verified these findings demonstrating that between 70% and 100% of patients treated with PUVA achieved clearing of psoriasis lesions (Griffiths et al, 2000; Spuls et al, 1997).
- The Agency for Healthcare Quality and Research (AHRQ) published a comparative effectiveness review of the biologic systemic agents compared to nonbiologic systemic agents or phototherapy on an individual drug level for the treatment of chronic plaque psoriasis. A total of five randomized clinical trials and four observational studies were identified. In summary, limited data exist that compare agents. Existing data were considered to be low strength of evidence, which in general favored the biological agents over the non-biologic agents (Lee et al, 2012).
- A Cochrane Review was conducted to compare the effectiveness, tolerability, and safety of topical treatments for chronic plaque psoriasis, relative to placebo, and to similarly compare vitamin D analogues (alone or in combination) with other topical treatments. A total of 177 randomized controlled trials with 34,808 participants were included. When used on the body, most vitamin D analogues were significantly more effective than placebo. Dithranol, combined treatment with vitamin D/corticosteroid, and tazarotene all performed significantly better than placebo. Head-to-head comparisons of vitamin D for psoriasis of the body against potent or very potent corticosteroids had mixed findings. For both the body and scalp psoriasis, combined vitamin D and corticosteroid treatment performed significantly better than vitamin D alone or corticosteroid alone. When applied to psoriasis of the scalp, vitamin D was significantly less effective than both potent corticosteroids and very potent corticosteroids. Vitamin D generally performed better than coal tar, but findings compared to dithranol were mixed. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause local adverse events, such as burning or irritation. No comparison of topical agents found a significant difference in systemic adverse effects (Mason et al, 2013).
- In addition to its FDA approval for the treatment of psoriasis, tazarotene, a topical retinoid agent, is also FDA-approved for the treatment of acne vulgaris. In a placebo-controlled trial by Bershad et al, tazarotene 0.1% gel was compared with tazarotene 0.1% gel plus a vehicle gel, or vehicle gel alone (Bershad et al, 2002). The primary efficacy endpoint, reduction in acne vulgaris lesions, was significant in both tazarotene treatment groups compared to the vehicle group (P=0.002). Clinical trials comparing tazarotene to other topical retinoid agents have shown conflicting results, with tazarotene being at equivalent or more effective than other topical retinoids (Pariser et al, 2008; Tanghetti et al, 2010; Shalita et al, 2005).
- The current guidelines for the management of psoriasis and psoriatic arthritis from the American Academy of Dermatology (AAD) recommend topical agents for mild to moderate psoriasis. Topical agents are also used adjunctively with ultraviolet light or systemic medications for resistant lesions or more severe disease. Topical corticosteroids are recommended as first-line treatment for most patients. Other topical agents included in the guidelines are vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, anthralin, coal tar, and combination products. Combination products include corticosteroid and salicylic acid, corticosteroid and vitamin D analogue, corticosteroid and tazarotene, and tacrolimus and salicylic acid. When used in conjunction with

ultraviolet radiation B or psoralen and UVA phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression (Gottleib et al, 2008; Menter et al, 2009[a]; Menter et al, 2009[b]; Menter et al, 2010; Menter et al, 2011).

- In a 2013 position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (AAD, 2013). Treatment needs vary depending on the severity of disease, body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences.
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (Thiboutot et al, 2009; Eichenfield et al, 2013).
    - According to the AAD, topical retinoids (e.g., tretinoin, adapalene, tazarotene) are recommended among the first-line treatment options for the management of acne (strength of recommendation: A [based on consistent and good-quality patient-oriented evidence]; level of evidence I [good-quality patient-oriented evidence, i.e., evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life], and II [limited-quality patient-oriented evidence]) (Zaenglein et al, 2016). Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions. The guidelines do not prefer one topical retinoid over another.
        - There are several head-to-head studies with retinoid products. Some support greater efficacy of tazarotene over adapalene and tretinoin, and adapalene over tretinoin, but the concentrations and formulations were varied. Overall, the limitations of the existing studies prohibit direct efficacy comparisons of topical retinoids.
    - According to the Medical Letter, topical retinoids can be used alone or in combination with antibiotics to treat both inflamed and noninflamed acne lesions, or for maintenance treatment of acne (Medical Letter, 2016).

SAFETY SUMMARY

- Topical calcipotriene is contraindicated in individuals with hypersensitivity to any components of the preparation. Additionally, calcipotriene administration in patients with vitamin D toxicity or hypercalcemia is also contraindicated. Calcipotriene should not be used for the treatment of the face, and the scalp solution is contraindicated in acute psoriatic eruptions. The most common adverse effects of calcipotriene are local effects including burning, pruritus, edema, peeling, stinging, dryness, skin irritation, and erythema. Contact dermatitis has been reported to occur with use of topical calcipotriene. Systemic side effects of vitamin D analogs, including hypercalcemia and parathyroid hormone suppression, are rare unless patients apply more than the recommended dosage of 100 g per week or have underlying renal disease or impaired calcium metabolism.
- There are no known contraindications to topical calcitriol. Among patients receiving laboratory monitoring, hypercalcemia was observed in 24% (18/74) of patients exposed to active drug and in 16% of (13/79) patients exposed to vehicle. This increase in calcium and albumin-adjusted calcium levels was <10% above the upper limit of normal. The effects of calcitriol on calcium metabolism have not been evaluated for treatment durations of >52 weeks. Additionally, increased absorption of calcitriol may occur with the use of occlusive dressings. Avoid exposure of treated areas to artificial or natural sunlight. The safety and efficacy of topical calcitriol in patients with disorders of calcium metabolism and patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated. The most common adverse effects include hypercalciuria, pruritus, and lab test abnormalities (not otherwise specified).
- There are no known contraindications to calcipotriene/betamethasone suspension, ointment, or foam. Caution should be used with all formulations in patients with elevated serum calcium levels. Additionally, hypothalamic-pituitary-adrenal axis suppression has occurred due to systemic absorption of the topical corticosteroid. Avoid exposure of treated areas to artificial or natural sunlight. Local adverse reactions such as atrophy, irritation, and allergic contact dermatitis are more likely to occur with occlusive use. Common adverse effects include pruritus, worsening of psoriasis, erythema, and burning sensation.
- Topical tazarotene is contraindicated in patients who are pregnant or who have a documented hypersensitivity reaction to any component of the formulation. Tazarotene should not be used on eczematous skin as severe irritation may occur. Additionally, increased photosensitivity may occur with concurrent

administration of fluoroquinolones, phenothiazines, sulfonamides, tetracyclines, and thiazides. Patients should be cautioned to take protective measures (e.g., sunscreens, protective clothing) against exposure to sunlight or ultraviolet light (e.g., tanning beds) until tolerance is determined. Excessive pruritus, burning, skin redness or peeling may occur. Discontinue tazarotene until skin integrity is restored, or reduce the dosing interval or switch to a lower concentration. The most common adverse effects include burning, erythema, and pruritus.

- Topical anthralin is contraindicated in acute or actively inflamed psoriatic eruptions. Additionally, the agent should not be used if there is a hypersensitivity to the active ingredient or any of its components. The most common side effects of anthralin are skin irritation and staining of lesional and adjoining skin, nails, and clothing.
- Acitretin is teratogenic and its use, therefore, is limited to male and female patients of nonchildbearing potential. Acitretin should only be considered for women of childbearing potential with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Other contraindications for acitretin include severe liver or kidney impairment, chronic elevation of lipid profile, and use in combination with methotrexate or tetracyclines. Potential adverse effects of acitretin include dry skin and mucus membranes, alopecia, skin peeling, pruritus, cheilitis, rhinitis, hyperlipidemia, liver toxicity, and teratogenicity. Periodic monitoring of bones, lipid profile, and eyes is recommended.
- Methoxsalen is contraindicated with a history of light sensitivity, melanoma, invasive squamous cell carcinoma or aphakia. Skin irritation, including severe edema, erythema, blistering, and exfoliative dermatitis, can occur during PUVA therapy. Pruritus and other dermatological effects may occur as well. Nausea and vomiting occurs in 10% of patients receiving methoxsalen, and central nervous system (CNS) effects including depression, dizziness, and headache have been reported. Patients who have received PUVA therapy should be monitored throughout their lives for the development of cutaneous malignancies.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Topical Therapy				
DRITHO-CREME (anthralin)	Cream: 1%	Treatment of psoriasis (quiescent or chronic): Cream: Apply once a day to psoriatic lesions for 5 to 10 minutes using the lowest strength possible for at least one week; may increase contact time up to 20 to 30 minutes as tolerated		Avoid spreading cream onto the forehead; remove by washing or showering. For scalp psoriasis, comb hair to remove scalar debris; wet and part hair; rub cream into lesions.
ZITHRANOL (anthralin)	Shampoo: 1%	Scalp Psoriasis: Apply onto wet scalp 3 to 4 times per week. Leave on scalp for 3 to 5 minutes and then rinse thoroughly.		
ZITHRANOL-RR (anthralin)	Cream: 1.2%	Plaque Psoriasis: Skin: Apply once a day. Start with short contact time (5 to 15 minutes) for at least 1 week. Increase stepwise to 30 minutes before removing cream by washing or showering. Scalp: Apply while hair is		Skin: Apply sparingly to the psoriatic lesions and rub gently and carefully into the skin. Scalp: Rub the cream well into the psoriatic lesions;

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		damp. At end of each period of contact, rinse hair and scalp thoroughly and then shampoo.		avoid applying to uninvolved scalp margins.
DOVONEX (calcipotriene)	Cream: 0.005%	Plaque psoriasis: Apply a thin layer to affected area 1 to 2 times per day and rub in completely.	Safety and effectiveness of DOVONEX cream have been demonstrated in patients treated for 8 weeks.	
SORILUX (calcipotriene)	Foam: 0.005%	Plaque psoriasis: Apply a thin layer twice daily to the affected areas and rub in gently and completely.		Avoid contact with the face and eyes.
Calcipotriene ointment	Ointment: 0.005%	Plaque psoriasis: Apply a thin layer to affected area 1 to 2 times per day and rub in gently and completely.		
Calcipotriene scalp solution	Solution: 0.005%	Severe Psoriasis of the scalp: Comb hair to remove scaly debris and apply twice daily, only to lesions, and rub in gently and completely.	Safety and efficacy have been demonstrated in patients treated for 8 weeks.	Do not spread to forehead. Keep well away from eyes. Avoid applying to uninvolved scalp margins.
VECTICAL (calcitriol)	Ointment: 3 mcg/g	Plaque psoriasis: Apply to affected areas twice daily, morning and evening.	The maximum weekly dose should not exceed 200 g.	Not for oral, ophthalmic, or intravaginal use.
ENSTILAR (calcipotriene/ betamethasone dipropionate)	Foam: 0.005%/ 0.064%	Plaque psoriasis: Apply to affected area once daily for up to 4 weeks.	Do not use more than 60 g every 4 days.	Do not use with occlusive dressings unless directed by a physician. Not for oral, ophthalmic, or intravaginal use. Avoid use on face, groin, axillae, or if skin atrophy is present at treatment site.
TACLONEX (calcipotriene/ betamethasone dipropionate)	Ointment: 0.005%/ 0.064% Topical Suspension: 0.005%/ 0.064%	Ointment: Psoriasis: Apply to affected areas once daily for up to 4 weeks. Topical Suspension: Plaque Psoriasis: Apply to affected areas once daily for up to 8 weeks.	Maximum weekly dose should not exceed 100 g for patients ≥18 years of age. For patients 12 to 17 years of age, maximum weekly use should not exceed 60 g.	Do not use on face, axillae, or groin. Do not use with occlusive dressings unless directed by a physician. Do not use if skin atrophy is present

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Treatment of >30% of body surface area is not recommended.	at treatment site. Shake topical suspension before use. Not for oral, ophthalmic, or intravaginal use.
TAZORAC (tazarotene)	Cream: 0.05%, 0.1% Gel: 0.05%, 0.1%	Psoriasis: Cream, gel: Apply a thin film to affected area once daily in the evening. Acne vulgaris for ages ≥12 years old: Cream (0.1%), gel (0.1%): Apply a thin film to affected area once daily in the evening.	Psoriasis: Start with 0.05% cream/gel, then increase to 0.1% if tolerated and medically indicated.	
Oral Agents				
SORIATANE (acitretin)	Capsules: 10 mg, 17.5 mg, 25 mg	Psoriasis: Initiate at 25 to 50 mg per day, given as a single dose with the main meal. Maintenance doses of 25 to 50 mg per day may be given dependent upon response to initial treatment.		
OXSORALEN (methoxsalen)	Capsules: 10 mg	Psoriasis: Take 2 hours before UVA exposure with food or milk according to following table: <30 kg: 10 mg 30-50 kg: 20 mg 51-65 kg: 30 mg 66-80 kg: 40 mg 81-90 kg: 50 mg 91-115 kg: 60 mg >115 kg: 70 mg	If weight changes during treatment, no change in dose is usually required. The number of doses per week will be determined by the schedule of UVA exposures. Dosages may be increased by 10 mg after the 15th treatment.	

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Topical Therapy					
DRITHO-CREME, ZITHRANOL, ZITHRANOL-RR (anthralin)	No data	Safety and efficacy have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
DOVONEX, SORILUX, calcipotriene ointment, calcipotriene scalp solution (calcipotriene)	DOVONEX, calcipotriene scalp solution: No differences in adverse events for subjects >65 years. However, greater sensitivity cannot be ruled out. SORILUX: Trials did not include sufficient numbers of subjects >65 years. Calcipotriene ointment: Severity of skin-related adverse events showed a significant difference for subjects >65 years.	Safety and efficacy have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
VECTICAL (calcitriol)	Trials did not include sufficient numbers of subjects >65 years.	Safety and efficacy have not been established.	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
ENSTILAR, TACLONEX (calcipotriene/ betamethasone)	No differences in safety and effectiveness for subjects >65 years; however, greater sensitivity cannot be ruled out.	Safety and efficacy have not been established in children <12 years (suspension, ointment).	No data	No data	Pregnancy category C* Unknown whether excreted in breast milk; use with caution. Do not apply to breast when nursing.
TAZORAC (tazarotene)	Cream: No overall differences in safety or effectiveness were observed between	Safety and efficacy have not been established in patients with	No data	No data	Pregnancy category X* Unknown

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	subjects >65 years and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out. Gel: Subjects >65 years of age had more adverse events and lower treatment success rates after 12 weeks.	psoriasis under the age of 18 years (cream) and patients with acne under the age of 12 years (cream, gel).			whether excreted in breast milk; use with caution.
Oral Therapy					
SORIATANE (acitretin)	Trials did not include sufficient numbers of subjects >65 years. Initial dose should be at the low end of the dosing range.	Safety and efficacy have not been established.	Plasma concen-trations significantly lower in end-stage renal failure.	Elevations of liver function tests (AST, ALT or LDH) were experienced by 1 in 3 patients. Perform LFTs prior to initiation and at 1- and 2-week intervals until stable.	Pregnancy category X* Do not use prior to or during nursing.
OXSORALEN (methoxsalen)	Trials did not include sufficient numbers of subjects >65 years. Initial dose should be at the low end of the dosing range. Use with caution, especially those with a pre-existing history of cataracts, cardiovascular conditions, kidney and/or liver dysfunction, or skin cancer.	Safety in children has not been established.	No data	Treat with caution since hepatic biotransfor-mation is necessary for drug urinary excretion.	Pregnancy category C* Unknown whether excreted in breast milk; discontinue nursing or discontinue drug.

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

CONCLUSION

- Numerous topical and systemic therapies are available for the treatment of psoriasis. Topical treatment is considered to be the safest option and is widely used for mild psoriasis, followed by systemic and phototherapies, which are used for moderate to severe psoriasis. Selection of medication must take into account severity of disease, thickness and scaling of the lesions, relevant comorbidities, patient preference, efficacy, and evaluation of individual patient response (AAD, 2013; Hsu et al, 2012; Menter et al, 2009[b]).

- Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. Drawbacks associated with topical corticosteroid treatment are local cutaneous side effects and more serious systemic side effects that are associated with long-term use over a large body surface area (Menter et al, 2011). Several agents have been developed and tested as monotherapy or in combination with topical corticosteroids in the hopes of reducing the duration of corticosteroid treatment.
- The vitamin D analogs, calcipotriene and calcitriol, are other first-line topical agents with proven efficacy in the treatment of psoriasis. Although less effective than topical corticosteroids, they are often used in combination with topical corticosteroids to enhance efficacy and reduce the risk of atrophy, especially over the long term. One potential advantage of calcitriol is that there are no known contraindications for use, whereas calcipotriene (alone, but not in combination with betamethasone) is contraindicated in patients with hypercalcemia and vitamin D toxicity and in acute or actively inflamed psoriatic lesions. Another possible advantage of calcitriol is that it has been shown to be better tolerated in sensitive skin fold areas as well as associated with less stinging, burning, edema and erythema (Weinstein et al, 2003; Zhu et al, 2007).
- The combination of calcipotriene and betamethasone (ENSTILAR and TACLONEX) has been evaluated in several studies for the treatment of psoriasis compared to placebo and to its individual components. Overall, results indicated that the combination product was more effective in reducing psoriasis area and severity index scores, and it increased the percentage of patients with clear or almost clear disease compared to either agent alone or placebo (Douglas et al, 2002; Guenthe et al, 2002, Kaufman et al, 2002; Kragballe et al, 2004; Papp et al, 2003; Parslew et al, 2005; Singh et al, 2000; van de Kerkhof et al, 2004; van de Kerkhof et al, 2005). The combination is available as a suspension, ointment, and foam.
- Tazarotene is the only retinoid agent that is FDA-approved for the treatment of psoriasis. Clinical trials have demonstrated its efficacy alone as well as in combination with other antipsoriatic agents. Guidelines recommend its use as an adjunct to topical corticosteroids (Menter et al, 2009[b]). No significant differences were observed between calcipotriene or calcitriol and tazarotene in several head-to-head studies (Guenther et al, 2000; Schiener et al, 2000; Tzung et al, 2005). Other topical preparations, including anthralin, have taken on more secondary roles and are particularly challenging as they stain clothing and skin.
- Of the systemic therapies, acitretin is the least effective as monotherapy and is therefore often used in conjunction with ultraviolet B or psoralen plus UVA phototherapy. Acitretin does not lead to immunosuppression or the associated risk of infection like biologic agents. Guidelines recommend the use of acitretin in combination with phototherapy as first-line treatment for psoriasis when not contraindicated, before resorting to other agents including methotrexate, cyclosporine, or biologic treatments (Lebwohl, 2001; Menter et al, 2009; Menter et al, 2010). Acitretin should not be used in women of childbearing potential.
- Methoxsalen and ultraviolet light (PUVA) is an effective method of treating psoriasis. PUVA is indicated in patients with moderate to severe psoriasis that is unresponsive to other forms of therapy or for lesions that are too extensive for topical treatment (Menter et al, 2010).
- In a position paper published by the AAD, psoriasis patients with moderate to severe psoriasis may avoid stepwise-therapy (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) and be moved to later line therapy based on disease severity (AAD, 2013). Consensus guidelines agree that the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life (AAD, 2013).
- Topical retinoids such as tazarotene are also effective in the treatment of acne vulgaris. Guidelines do not recommend one retinoid over another but do generally recommend these agents as a first-line combination option (Thiboutot et al, 2009; Zaenglein et al, 2016; Eichenfield et al, 2013).

REFERENCES

- American Academy of Dermatology and AAD Association. Position Statement on Treatment of Psoriatic Patients. April 27, 2013. Available at: http://www.aad.org/Forms/Policies/Uploads/PS/PS%20on%20Treatment%20of%20Psoriatic%20Patients.pdf Accessed March 8, 2017.
- Bershad S, Kranjac Singer G, Parente JE, et al. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. Arch Dermatol. 2002;138(4):481-9.
- Bowman P, Maloney J, Koo J. Combination of calcipotriene (Dovonex) ointment and tazarotene (Tazorac) gel versus clobetasol ointment in the treatment of plaque psoriasis: a pilot study. J Am Acad Dermatol. 2002;46(6):907-13.
- Buckley C, Hoffmann V, Shapiro J, et al. Calcipotriol plus betamethasone Dipropionate Scalp Formulation Is Effective and Well Tolerated in the Treatment of Scalp Psoriasis: A Phase II study. Dermatology. 2008; 217:107-13.
- Calcipotriene ointment prescribing information. Glenmark Pharmaceuticals Inc. Mahwah, NJ. May 2015.
- Calcipotriene solution prescribing information. Impax Generics. Hayward, CA. September 2015.
- De Jong E, Mork N, Seijger M, et al. The combination of calcipotriol and methotrexate compared with methotrexate and vehicle in psoriasis: results of a multicentre placebo-controlled randomized trial. Br J Dermatol. 2003;148:318-25.

- Douglas W, Poulin Y, Decroix J, et al. A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone dipropionate or calcipotriol in psoriasis vulgaris. Acta Derm Venereol. 2002;82:131-5.
- DOVONEX cream prescribing information. LEO Pharma, Inc. Parsippany, NJ. March 2015.
- DRITHRO-CRÈME (anthralin) prescribing information. Summers Laboratories. Collegeville, PA. October 2014.
- DRUGS@FDA.com [database on the internet]. Rockville, MD: U.S. Food and Drug Administration. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 8, 2017.
- Dubertret L, Wallach D, Souteyrand P, et al. Efficacy and safety of calcipotriol (MC 903) ointment in psoriasis vulgaris. A randomized, double-blind, right/left comparative, vehicle-controlled study. J Am Acad Dermatol 1992;27:938-8.
- Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne. Pediatrics. 2013;131:S163-186.
- ENSTILAR foam prescribing information. Leo Pharma Inc. Parsippany, NJ. November 2016.
- Feldman SR, Matheson R, Bruce S, et al. Efficacy and safety of calcipotriene 0.005% foam for the treatment of plaque-type psoriasis. Am J Clin Dermatol. 2012;13:261-271.
- Feldman SR, Mills M, Brundage T, et al. A multicenter, randomized, double-blind study of the efficacy and safety of calcipotriene foam, 0.005% vs vehicle foam in the treatment of plaque-type psoriasis of the scalp. J Drugs Dermatol. 2013;12:300.
- Fredriksson T. A comparative study of dithranol cream, 0.25% and 0.1%, and dithranol ointment 0.25% in the treatment of psoriasis. Pharmatherapeutica. 1983;3:496-8.
- Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;58(5):851-64.
- Griffiths CE, Clark CM, Chalmers RJ, et al. A systematic review of treatments for severe psoriasis. Health Technol Assess. 2000;4:1-125.
- Guenther L, Cambazard F, van de Kerkhof P, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. Br J Dermatol. 2002;147:316-23.
- Guenther L, Poulin Y, Pariser D. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. Clin Ther. 2000;22(10):1225-38.
- Henseler T, Honigsmann H, Wolff K, et al. Oral 9-methoxypsoralen photochemotherapy of psoriasis: The European PUVA study: a cooperative study among 18 European centres. Lancet. 1981;1(8225):853-857.
- Highton A, Quell J. calcipotriene ointment 0.005% for psoriasis: a safety and efficacy study. Calcipotriene Study Group. J Am Acad Dermatol. 1995;32:67-72.
- Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148(1):95-102.
- Jemec G, Ganslandt C, Ortonne J, et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: A randomized, double-blind, controlled trial. J Amer Acad Dermatol. 2008; 59(3):455-63.
- Jones SK, Campbell WC, Mackie RM. Out-patient treatment of psoriasis: short contact and overnight dithranol therapy compared. Br J Dermatol. 1985;113:331-7.
- Kaufman R, Bibby A, Bissonnette R, et al. A new calcipotriol/betamethasone dipropionate formulation (Daivobet™) is an effective once-daily treatment for psoriasis vulgaris. Dermatology. 2002;205:389-93.
- Kragballe K, Hoffmann V, Ortonne JP, et al. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol. 2009; 161:159-66.
- Kragballe K, Noerrelund K, Lui H, et al. Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. Br J Dermatol. 2004;150:1167-73.
- Lebwohl M, Drake L, Menter A, et al. Consensus conference: Acitretin in combination with UVB or PUVA in the treatment of psoriasis. J Am Acad Dermatol. 2001;45(4):544-553.
- Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 µg/g ointment in the management of mild to moderate plaque psoriasis: Results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. J Drugs Dermatol. 2007 April;6(4):428-35.
- Lebwohl MG, Breneman DL, Goffe BS, et al. Tazarotene 0.1% gel plus corticosteroid cream in the treatment of plaque psoriasis. J Am Acad Dermatol. 1998;39(4 Pt 1):590-6.
- Lee S, Coleman CI, Limone B, et al. Biologic and nonbiologic systemic agents and phototherapy for treatment of chronic plaque psoriasis. Comparative Effectiveness Review No. 85. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No.12(13)-EHC144-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1326. Accessed March 8, 2017.
- Luger TA, Cambazard F, Larsen FG, et al. A Study of the Safety and Efficacy of Calcipotriol and Betamethasone Dipropionate Scalp Formulation in the Long-Term Management of Scalp Psoriasis. Dermatology. 2008; 217:321-8.
- Mason AR, Mason J, Cork M, et al. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev. 2013; Mar 28;3:CD005028. doi: 10.1002/14651858.CD005028.pub3.
- Melski J, Tannenbaum L, Parrish J, et al. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. J Invest Dermatol. 1977;68(6):328-335.
- Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3: Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009[b];60:643-59.
- Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5: Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62:114-35.
- Menter A, Korman NJ, Elmets CA, et al. American Academy of Dermatology Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65:137-74.
- Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009[a];61:451-85.

- Olsen EA, Weed WW, Meyer CF, et al. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. J Am Acad Dermatol. 1989;21(4 Pt 1): 681-686.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Rockville, MD: U.S. Food and Drug Administration. Available from: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 1, 2017.
- Ortonne JP, Ganslandt C, Tan J, et al. Quality of life in patients with scalp psoriasis treated with calcipotriol/betamethasone dipropionate scalp formulation: a randomized controlled trial. Eur Acad Dermatol Venereol. 2009; 23:919-26.
- Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3mcg/g ointment and calcipotriol 50mcg/g ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. Br J Dermatol. 2003 Feb; 148(2):326-33.
- OXSORALEN-ULTRA prescribing information. Valeant Pharmaceuticals. Aliso Viejo, CA. February 2015.
- Ozkan I, Kose O, Ozmen I, et al. Efficacy and safety of non-laser, targeted UVB phototherapy alone and in combination with psoralen gel or calcipotriol ointment in the treatment of localized, chronic, plaque-type psoriasis. Int J Derm. 2012;51:609-13.
- Papp K, Guenther L, Boyden B, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. J Am Acad Dermatol. 2003;48(1):48-5.
- Pariser D, Colon LE, Johnson LA, Gottschalk RW. Adapalene 0.15 gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. J Drugs Dermatol. 2008;7(6 Suppl):s18-23.
- Parslew R, Traulsen J. Efficacy and local safety of a calcipotriol/betamethasone dipropionate ointment in elderly patients with psoriasis vulgaris. Eur J Dermatol. 2005;15(1):37-9.
- Reygagne P, Mrowietz U, Decroix J, et al. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J Dermatologic Treatment. 2005;16:31-6.
- Rim JH, Park JY, Choe YB, et al. The efficacy of calcipotriol + acitretin combination therapy for psoriasis: Comparison with acitretin monotherapy. Am J Clin Dermatol. 2003;4(7):507-510.
- Roenigk HH Jr, Farber E, Storrs F, et al. Photochemotherapy for psoriasis: a clinical cooperative study of PUVA-48 and PUVA-64. Arch Dermatol.1979;115(5):576-579.
- Schiener R, Behrens-Williams S, Pillekamp H, et al. Calcipotriol vs. tazarotene as combination therapy with narrowband ultraviolet B (311 nm): efficacy in patients with severe psoriasis. Br J Dermatol. 2000;143:1275-8.
- Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. J Am Acad Dermatol. 1996;34:482-5.
- Singh S, Reddy D, Pandey S. Topical therapy for psoriasis with the use of augmented betamethasone and calcipotriene on alternate weeks. J Am Acad Dermatol. 2000;43(1):61-5.
- SORIATANE prescribing information. Stiefel Laboratories. Research Triangle Park, NC. May 2015.
- SORILUX prescribing information. Stiefel Laboratories. Research Triangle Park, NC. September 2013.
- Spuls PI, Witkamp L, Bossuyt PM, et al. A systematic review of five systemic treatments for severe psoriasis. Br J Dermatol. 1997;137:943-9.
- TACLONEX ointment prescribing information. Leo Pharma. Parsippany, NJ. January 2017.
- TACLONEX suspension prescribing information. Leo Pharma. Parsippany, NJ. January 2017.
- Tanghetti E, Dhawan S, Green L, et al. Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. J Drugs Dermatol. 2010;9(5):549-58.
- TAZORAC cream prescribing information. Allergan. Irvine, CA. December 2013.
- TAZORAC gel prescribing information. Allergan. Irvine, CA. May 2014.
- Thaci D, Daiber W, Boehncke W, et al. Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety, and acceptance in 3,396 patients. Dermatology. 2001;203:153-6.
- The Medical Letter. Drugs for Acne. Med Let. 2016;58(1487):13-16.
- Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol. 2009;60:S1-50.
- Torras H, Aliaga A, Lopez-Estebaranz J, et al. A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. J Dermatol Treat. 2004;15:98-103.
- Tosti A, Ricotti C, Romanelli P, et al. Evaluation of the efficacy of acitretin therapy for nail psoriasis. Arch Dermatol. 2009;145(3):269-271.
- Tzung T, Wu J, Hsu N, et al. Comparison of tazarotene 0.1% gel plus petrolatum once daily versus calcipotriol 0.005% ointment twice daily in the treatment of plaque psoriasis. Acta Derm Venereol. 2005;85:236-9.
- Usatine RP, Marcelin L. Psoriasis. First Consult Article. Last Updated: August 28, 2013. Available at: http://www.clinicalkey.com. Accessed March 8, 2017.
- van de Kerkhof P, Wasel N, Kragballe K, et al. A two-compound product containing calcipotriol and betamethasone dipropionate provides rapid, effective treatment of psoriasis vulgaris regardless of baseline disease severity. Dermatology. 2005;210:294-9.
- van de Kerkhof P. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet/Dovobet) on the quality of life in patients with psoriasis vulgaris: a randomized controlled trial. Br J Dermatol. 2004;151:663-8.
- van de Kerkhof PC, Cambazard F, Hutchinson PE, et al. The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998;138(1):84-89.
- van de Kerkhof PCM, Hoffmann V, Anstey A, et al. A new scalp formulation of calcipotriol plus betamethasone dipropionate compared with each of its active ingredients in the same vehicle for the treatment of scalp psoriasis: a randomized, double-blind, controlled trial. Br J Dermatol. 2009; 160:170-6.
- VECTICAL prescribing information. Galderma. Fort Worth, TX. July 2012.
- Veronikis I, Malabanan A, Holick M. Comparison of calcipotriene (Dovonex) with a coal tar emulsion (Exorex) in treating psoriasis in adults: a pilot study. Arch Dermatol. 1999;135(4):474-5.
- Villasenor-Park J, Wheeler D, Grandinetti L. Psoriasis: Evolving treatment for a complex disease. Cleveland Clinic Journal of Medicine. 2012;79:413-423.
- Weinstein GD, Koo JY, Krueger GG, et al; Tazarotene Cream Clinical Study Group. Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. J Am Acad Dermatol. 2003;48(5):760-7.

- Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. J Am Acad Dermatol. 1997;37(1):85-92.
- Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74:945-73.
- Zhu X, Wang B, Zhao G, et al. An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3 microg/g ointment vs. calcipotriol 50 microg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol. 2007;21(4):466-72.
- ZITHRANOL Shampoo prescribing information. Elorac. Vernon Hills, IL. October 2011.
- ZITHRANOL-RR prescribing information. Elorac. Vernon Hills, IL. July 2008.

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Therapeutic Class Overview
Antivirals, Topical

INTRODUCTION

- Herpes simplex virus 1 (HSV-1) and HSV-2 cause a wide variety of illnesses, including mucocutaneous infections, central nervous system infections, and infections of the visceral organs. The two most common cutaneous manifestations of the HSV infection are orolabial and genital herpes. Orolabial herpes, which presents most commonly as cold sores, is the most prevalent form of mucocutaneous herpes infection, with 57 to 80% of adults in the United States (US) showing serologic evidence of having been infected by HSV-1 (Cernik et al, 2008). Both viral subtypes can cause orolabial or genital infections and are clinically indistinguishable; however, cold sores are most often caused by HSV-1, and genital herpes is most often caused by HSV-2.
- Herpes simplex is typically transmitted through close contact with a person who is shedding virus at a peripheral site, at a mucosal surface, or in genital or oral secretions. Contact must involve mucous membranes or open or abraded skin. Following transmission, the initial infection is associated with systemic signs and symptoms and involves both mucosal and extramucosal sites. Initial infections are also associated with higher complication rates and have a longer duration of symptoms and viral shedding from lesions. After inoculation and initial infection, HSV settles into nerves near the spine and becomes latent. From there, the virus can travel along the nerves, back to the skin and either reactivate (ie, new blisters or lesions are formed) or shed (ie, no new blisters or lesions are formed). The exact mechanism of reactivation is not completely understood; however, the frequency depends on the severity and duration of the initial episode, the infecting serotype (ie, HSV-1 or -2), and the host. In contrast to initial infections, associated symptoms, signs, and anatomic sites of recurrent infections are typically localized to a defined mucocutaneous site. Recurrent infections may also be associated with prodromal symptoms, which can occur in the absence of lesions, and vary from mild tingling sensations to shooting pains. Recurrent labial herpes infection affects approximately one-third of the US population. Typically, patients experience one to six episodes per year (Cernik et al, 2008).
- Genital herpes is one of the most common viral sexually transmitted diseases (STDs) in the world. In the US, between the periods 1988 to 1994 and 1999 to 2004, the overall prevalence of HSV-2, the most common cause of genital herpes, declined 17%, from 21.3% of males and females infected with the virus to 17.6%. The prevalence in men declined most dramatically, from 17.3% to 11.2%, a 35% decrease (Xu et al, 2006). Overall HSV-2 seroprevalence in 2005 to 2010 was 15.7%, suggesting a plateau in infection rates (Bradley et al, 2014). Most people infected with HSV-2 have not been diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. After resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, causing recurrent (often less severe) outbreaks.
- Before the introduction of acyclovir as an antiviral drug in the early 1980s, cutaneous HSV infection was managed with drying agents and other local care. Today, treatment options include multiple oral, intravenous, and topical antiviral agents. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection (Emmert, 2000). Topical antivirals have minimal clinical benefit in genital herpes, and use should be discouraged (CDC, 2015). No antiviral agent currently available will eradicate HSV, and thus treatment is aimed at managing rather than curing the disease.
- This review will focus on the topical agents for HSV.
- Medispan class: Antivirals, Topical and Antivirals, Topical Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Abreva (docosanol)*	-
Denavir (penciclovir)	-
Xerese (acyclovir/hydrocortisone)	-
Zovirax (acyclovir cream)	-
Zovirax (acyclovir ointment)	✔

* Over-the-counter (OTC) product

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Abreva (docosanol)	Denavir (penciclovir)	Xerese (acyclovir/ hydrocortisone)	Zovirax (acyclovir cream)	Zovirax (acyclovir ointment)
Early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time (age ≥ 6 years)	-	-	✔	-	-
Management of initial genital herpes	-	-	-	-	✔
Management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients	-	-	-	-	✔
Treatment of cold sores/fever blisters on face or lips to shorten healing time and duration of symptoms (age ≥ 12 years)	✔	-	-	-	-
Treatment of recurrent herpes labialis (cold sores) (age ≥ 12 years)	-	✔	-	✔ *	-

* In immunocompetent patients

(Prescribing information: Abreva, 2017; Denavir, 2013; Xerese, 2014; Zovirax cream, 2017; Zovirax ointment, 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Conflicting results have been observed among clinical trials with topical antivirals. In two placebo-controlled studies evaluating the efficacy of a five-day treatment regimen of acyclovir ointment for the treatment of genital herpes, viral shedding was reduced in acyclovir treated patients, but no difference in healing time was demonstrated between groups (Luby et al, 1984; Reichman et al, 1983). Studies evaluating the efficacy of a regimen with duration greater than five days showed that acyclovir 5% ointment significantly reduced the duration of viral shedding from genital lesions, mean duration of local pain or itching, mean time to healing of lesions, and duration of new lesion formation when compared to placebo (Corey et al, 1982; Kinghorn et al, 1983). These studies also showed a significant decrease with acyclovir ointment in the average time to crusting and healing of lesions and duration for all symptoms in patients with recurrent episodes.
- When the efficacy of acyclovir 5% cream was evaluated against placebo for the treatment of genital herpes, only a significant decrease in the duration of itching was seen in the acyclovir group (Kinghorn et al, 1986).
- Studies involving acyclovir 5% cream for the treatment of recurrent herpes labialis have demonstrated a significantly shorter mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo (Gibson et al, 1986; Raborn et al, 1997; Shaw et al, 1985; Spruance et al, 1984; Spruance et al, 2002). However, changes in healing time of lesions and the number of episodes per month were not found to be significantly different.
- When compared to placebo, patients with herpes labialis treated with penciclovir 1% cream were shown to have significant decreases in overall healing time, resolution of lesion pain, and resolution of symptoms including itching, tingling, burning, numbness, and tenderness (Boon et al, 2000; Raborn et al, 2002; Spruance et al, 1997). Patients treated with penciclovir were also shown to have a significantly higher proportion of cases healed at 6 and 8 days. In randomized, controlled trials by Femiano et al, and Lin et al, penciclovir 1% cream was compared to acyclovir cream (5% and 3%, respectively). Penciclovir showed significantly shorter time to crusting. However, the percent of patients cured at seven days was not significantly different (Femiano et al, 2001; Lin et al, 2002).

- In a multicenter, randomized, placebo-controlled trial (N=737), docosanol cream was shown to reduce the median time to complete healing for all lesions (4.08 days vs. 4.8 days in the placebo group; 95% confidence interval [CI], 2 to 22; p = 0.008) (Sacks et al, 2001). Comparative data are not available for this over-the-counter product.
- The combination cream Xerese (acyclovir 5%/hydrocortisone 1%) was shown to reduce the occurrence of ulcerative lesions in patients with a history of herpes labialis compared to placebo in a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. Acyclovir/hydrocortisone reduced the progression of cold sores to ulcerative lesions and significantly reduced the lesion area compared with acyclovir and placebo (Hull et al, 2011). The safety of acyclovir/hydrocortisone was also demonstrated in adolescents with herpes labialis (Strand et al, 2012). Adverse events were similar to other clinical trials of the combination cream in adults.
- The topical antivirals have not been well studied in the immunocompromised patient population. A study involving immunocompromised patients with herpes simplex virus who received acyclovir 5% ointment or placebo demonstrated that acyclovir significantly accelerated the clearance of virus, as well as significantly shortened the time to resolution of pain and total healing (Whitley et al, 1984).

CLINICAL GUIDELINES

- Most national guidelines, including those published by the CDC, report that the topical antiviral agents offer minimal clinical benefit and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, and valacyclovir) (ACOG, 2004; CDC, 2015; Panel on Opportunistic Infections, 2015). However, no studies have been conducted which directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

SAFETY SUMMARY

- Topical antivirals should not be applied to the eye.
- Safety and efficacy of the topical antivirals have not been established in patients with immunosuppression.
- Adverse effects are mostly local in nature. Common adverse events include application site reaction, dryness, burning or stinging with application, and pruritus.
- Due to the topical application of these products, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Abreva (docosanol)	10% cream	Topical	5 times daily
Denavir (penciclovir)	1% cream	Topical	Every 2 hours while awake
Xerese (acyclovir/hydrocortisone)	5%/1% cream	Topical	5 times daily
Zovirax (acyclovir cream)	5% cream	Topical	5 times daily
Zovirax (acyclovir ointment)	5% ointment	Topical	6 times daily

See the current prescribing information for full details

CONCLUSION

- A total of five topical antivirals are FDA-approved. Denavir (penciclovir), Zovirax (acyclovir) cream and Xerese (acyclovir/hydrocortisone) are indicated for the treatment of recurrent herpes labialis. Abreva (docosanol) is an over-the-counter product indicated for the treatment of cold sores/fever blisters on the face or lips and to shorten the healing time and duration of symptoms. The only product in the class that is available generically, acyclovir ointment, is indicated for the initial treatment of genital herpes and in limited non-life-threatening mucocutaneous HSV infections in immunocompromised patients.
- The topical antiviral agents have demonstrated efficacy compared to placebo for their FDA-approved indications. They are generally safe with no significant drug interactions and limited adverse events.
- Head-to-head trials for the treatment of oral and/or genital herpes simplex have not consistently demonstrated superiority of one product over another. In a comparison trial in the treatment of herpes labialis, penciclovir cream resulted in a quicker time to crusting and cessation of pain compared to acyclovir; however, there was no significant difference in time to healing (Femiano et al, 2001). Lin et al also compared penciclovir and acyclovir in the treatment of

herpes labialis, and found that there was no significant difference in clinical cure rates and time to healing (Lin et al, 2002).

- Most national guidelines, including those published by the CDC, report that the topical antiviral agents offer minimal clinical benefit and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, valacyclovir) (ACOG, 2004; CDC, 2015; Panel on Opportunistic Infections, 2015). However, no studies have been conducted that directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

REFERENCES

- Abreva packaging. GlaxoSmithKline. Moon Township, PA. April 2017.
- American College of Obstetricians and Gynecologists. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists, number 57, November 2004. Gynecologic herpes simplex virus infections. Obstet Gynecol. 2004 Nov;104(5 Pt 1):1111-8.
- Boon R, Goodman JJ, Martinez J, et al. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. Clin Ther. 2000;22(1):76-90.
- Bradley H, Markowitz LE, Gibson T, et al. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. J Infect Dis. 2014;209(3):325-33.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR. 2015 June 5;64(3):1-140. Available from: http://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed May 5, 2017.
- Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidenced-based review. Arch Intern Med. 2008; 168(11):1137-1144. doi:10.1001/archinte.168.11.1137.
- Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Am J Med. 1982;73(1A):326-34.
- Denavir prescribing information. Prestium Pharma, Inc. Newtown, PA. September 2013.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 5, 2017.
- Emmert DH. Treatment of common cutaneous herpes simplex virus infections. Am Fam Phys. 2000;61(6):1697-708.
- Femiano F, Gombos F, Scully C, et al. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir (aciclovir). Oral Dis. 2001;7:31-3.
- Gibson JR, Klaber MR, Harvey SG, et al. Prophylaxis against herpes labialis with acyclovir cream—a placebo-controlled study. Dermatologica. 1986;172:104-7.
- Hull CM, Harmenberg J, Arlander E, et al. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. J Am Acad Dermatol. 2011 Apr;64(4):696.e1-11. doi: 10.1016/j.jaad.2010.08.012.
- Kinghorn GR, Abeywickreme I, Jeavons M, et al. Efficacy of combined treatment with oral and topical acyclovir in first episode genital herpes. Genitourin Med. 1986;186-8.
- Kinghorn GR, Turner EB, Barton IG, et al. Efficacy of topical acyclovir cream in first and recurrent episodes of genital herpes. Antiviral Res. 1983;3:291-301.
- Lin L, Chen XS, Cui PG, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double blind, multicenter, acyclovir-controlled trial. J Dermatolog Treat. 2002;13:67-72.
- Luby JP, Gnann JW Jr, Alexander WJ, et al. A collaborative study of patient-initiated treatment of recurrent genital herpes with topical acyclovir or placebo. J Infect Dis. 1984;150:1-6.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 5, 2017.
- Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institute of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Updated September 17, 2015. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 5, 2017.
- Raborn GW, Martel AY, Grace MG, et al. Herpes labialis in skiers: randomized clinical trial of acyclovir cream versus placebo. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84:641-5.
- Raborn GW, Martel AY, Lassonde M, et al, for the Worldwide Topical Penciclovir Collaborative Study Group. Effective treatment of herpes simplex labialis with penciclovir combined results of two trials. J Am Dent Assoc. 2002;133:303-9.
- Reichman RC, Badger GJ, Guinan ME, et al. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J Infect Dis. 1983;147(2):336-40.
- Sacks SL, Thisted RA, Jones TM, et al. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. J Am Acad Dermatol. 2001; 45:222-30.
- Shaw M, King M, Best JM, et al. Failure of acyclovir cream in treatment of recurrent herpes labialis. Br Med J. 1985;291:7-9.
- Spruance SL, Crumpacker CS, Schnipper LE, et al. Early, patient-initiated treatment of herpes labialis with topical 10% acyclovir. Antimicrob Agents Chemotherapy. 1984;25:553-5.
- Spruance SL, Nett R, Marbury T, et al. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Antimicrob Agents Chemother. 2002;46(7):2238-43.
- Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. JAMA. 1997;277(17):1374-9.

- Strand A, Böttiger D, Gever LN, et al. Safety and tolerability of combination acyclovir 5% and hydrocortisone 1% cream in adolescents with recurrent herpes simplex labialis. Pediatr Dermatol. 2012 Jan-Feb;29(1):105-10.
- Whitley RJ, Levin M, Barton N, et al. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. J Infect Dis. 1984;150(3):323-9.
- Xerese prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. January 2014.
- Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964-73.
- Zovirax cream prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. January 2017.
- Zovirax ointment prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. January 2017.

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Therapeutic Class Overview
Scabicides and Pediculicides

INTRODUCTION

- Scabies and pediculosis are infestations of the skin caused by ectoparasites. Scabies is caused by the parasitic mite *Sarcoptes scabiei* and often results in an intense pruritic eruption and itching. Pediculi or lice can cause infestations either on the head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), or the pubic region (*Phthirus pubis*). These skin conditions are common causes of skin rash and pruritus (Roos et al, 2001; Wendel et al, 2002). Head lice infestation crosses all social and geographic boundaries and generally affects children, primarily females, aged three to 12 years (Feldmeier, 2012). Scabies occur in both sexes, at all ages, and in all ethnic and socioeconomic groups; however, one epidemiologic study reported a higher prevalence in urban areas among women and children (Chosidow, 2006; Downs et al, 1999). The ideal agent for the treatment of head lice is one with high pediculicidal (capable of killing lice) and ovicidal (capable of killing eggs) activity with minimal toxicity (Villegas et al, 2012).
- The topical agents indicated for the management of scabies and head lice are listed in Table 1. All of the agents included in this review are Food and Drug Administration (FDA)-approved for the treatment of head lice with the exception of EURAX® (crotamiton), which is only indicated to treat scabies. Lindane lotion indicated to treat scabies has been discontinued; the shampoo is still available.
- The pediculicidal effects of most of these agents result from their neurotoxic effects on lice. These agents except benzyl alcohol cause periods of central nervous system hyperexcitation, resulting in paralysis and ultimately death of the lice. ULESFIA® (benzyl alcohol) is unique in that it disables the breathing structure of the lice, resulting in asphyxiation rather than neuroexcitation (ULESFIA prescribing information, 2015). Neurotoxic insecticides rely on the nervous system to exert their effect; therefore, newborn larvae are not susceptible to these agents since they do not develop a nervous system for several days after hatching. This presents a challenge for eliminating lice with a single treatment because the infestation typically includes lice from all stages of the life cycle, including newly hatched eggs.
- RID® (pyrethrins) and NIX® (permethrin) are pediculicidal, but not ovicidal, and therefore require nit combing and retreatment in seven to ten days to eradicate the infestation. Benzyl alcohol is not ovicidal and also requires a second treatment, but resistance is unlikely due to its unique mechanism of action. Malathion is both pediculicidal and ovicidal, but it is malodorous, requires 8 to 12 hours of application and is highly flammable. Lindane is neurotoxic and is not recommended as an initial treatment option (Lindane prescribing information, 2011). SKLICE® (ivermectin) and NATROBA® (spinosad) are pediculicidal but not ovicidal (NATROBA prescribing information, 2014). Topical ivermectin is approved as a single application product only (SKLICE prescribing information, 2016).
- Some data suggest a growing resistance to permethrin in the United States, with recent studies stating that the effectiveness of permethrin has declined to 25% and resistance to pyrethrins is widespread. (Koch et al, 2016, The Medical Letter, 2016). However, both the Centers for Disease Control and Prevention (CDC) as well as the American Academy of Pediatrics (AAP) continue to recommend permethrin as first-line antiparasitic therapy for treatment of both lice and scabies. For the treatment of head lice, therapy should be initiated with permethrin 1% or pyrethrins when resistance is not suspected. Malathion (in patients who are 6 years of age or older) and benzyl alcohol (in children older than 6 months) may be used when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Per the AAP, spinosad and ivermectin might prove helpful in difficult cases, but the cost of these preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP for use as treatment of head lice (Downs et al, 1999; CDC, 2015; CDC, 2016a; CDC, 2016b; Devore, Schultz, 2015).
- Medispan class: Scabicides and pediculicides and scabicide combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EURAX (crotamiton)	Ranbaxy	07/06/1949	-
Lindane (gamma-hexachlorocyclohexane)*	various	1947	✔
NATROBA (spinosad)	ParaPRO; Macoven	01/18/2011	✔
OVIDE® (malathion)	various	08/02/1982	✔
Permethrin* (ACTICIN® 5%, ELIMITE 5%, NIX® COMPLETE LICE SYSTEM®*, NIX CRÈME RINSE®*)	various	various	✔
Piperonyl butoxide and pyrethrins† (LICIDE COMPLETE LICE TREATMENT KIT®†, PRONTO®†, RID®†)	various	various	✔
SKLICE (ivermectin)	Sanofi	02/07/2012	-
ULESFIA (benzyl alcohol)	Shionogi	04/09/2009	-

*Lindane shampoo is available; the lotion formulation has been discontinued.
†Over-the-counter product is available in at least one dosage form or strength. Not all product options are listed as there are a number of over-the-counter options.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drugs	Scabies	Head Lice	Head and Pubic Lice	Head, Body, and Pubic Lice
EURAX (crotamiton)	✔			
Lindane			✔ *	
Malathion		✔ †		
NATROBA (spinosad)		✔ ‡		
Permethrin	✔ §‖	✔ ¶‖		
Piperonyl butoxide and pyrethrins				✔ **
SKLICE (ivermectin)		✔ ‡		
ULESFIA (benzyl alcohol)		✔ ‡		

*Lindane shampoo is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head or pubic lice.
† In patients ≥6 years of age.
‡ In patients ≥6 months of age.
§ Permethrin cream is indicated for the treatment of scabies.
‖ In patients ≥2 months of age
¶ Permethrin lotion/cream rinse and liquid are indicated for the treatment of head lice.
**For pyrethrins, approved in patients ≥2 years of age.

(Prescribing information: EURAX, 2012; Lindane, 2011; NATROBA, 2014; OVIDE, 2013; SKLICE, 2016; ULESFIA, 2015; Clinical Pharmacology, 2017)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Scabies

- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and lindane (Amer et al, 1992; Haustein et al, 1989; Schultz et al, 1990; Taplin et al, 1986b; Taplin et al, 1990; Zargari et al, 2006). In the largest study (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin compared to lindane; however, the difference was not statistically significant (Schultz et al, 1990). In a single-blind, randomized controlled trial comparing ivermectin to crotamiton (N=340), two applications of ivermectin were as effective as a single application of crotamiton cream for the treatment of scabies at two weeks. After repeating therapy, ivermectin was superior to crotamiton cream at four weeks follow-up (Goldust et al, 2014).

- Both lindane and permethrin have also been compared to oral ivermectin for the treatment of scabies. Numerous studies have demonstrated a significantly lower cure rate after four weeks with lindane compared to oral ivermectin (Goldust et al, 2013; Madan et al, 2001; Mohebbipour et al, 2013). However, another study found similar efficacy between the two agents at day 15 and 29 after treatment (Chouela et al, 1999). Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (Usha et al, 2000).

Lice

- Benzyl alcohol has been evaluated in two multicenter, randomized, double-blind, vehicle-controlled studies in patients (six months and older) with an active head lice infestation (N=628). In both studies, two applications of benzyl alcohol were associated with a significantly greater chance of treatment success (zero live lice 14 days following final treatment), compared to vehicle (P<0.001). The absolute difference in treatment success rates in study I was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7%) and 48.8% (95% CI, 31.1 to 62%) in study II, again in favor of benzyl alcohol. In both studies, there was a lower incidence of treatment failure associated with benzyl alcohol compared to vehicle (3.3 vs 83.6% and 14.3 vs 60.7% in studies I and II, respectively; P<0.001 for both) (Meinking et al, 2010).
- Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (Brandenburg et al, 1986; Bowerman et al, 1987; Kalter et al, 1987; Taplin et al, 1986a;). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (P>0.01) (Carson et al, 1988; DiNapoli et al, 1988). In multiple studies, malathion has been reported to be pediculicidal and ovicidal or had higher rates of cure when compared to permethrin (Meinking et al, 2004; Meinking et al, 2007; Roberts et al, 2000).
- Two identical, vehicle-controlled studies demonstrating the safety and efficacy of ivermectin lotion in the treatment of head lice were completed in 781 patients (six months and older) with head lice. The two studies showed that a higher percentage of patients treated with one application of ivermectin lotion, without nit combing, were treatment responders (free of live lice at day two and through day eight to the final evaluation at day 15) following a single application (combined study results for day 2: 94.9% vs 31.3%, respectively; day 8: 85.2% vs 20.8%, respectively; day 15: 73.8% vs 17.6%, respectively; P<0.001 for each comparison)(Pariser et al, 2012).
- Spinosad has been evaluated in two randomized, active-controlled trials of 1,038 patients aged six months or older with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of lice-free patients compared to permethrin with nit combing (P<0.001 for both trials). Moreover, the majority of patients treated with spinosad required only one course of treatment, compared to the majority of permethrin-treated patients who required two courses of treatment (P values not reported)(Stough et al, 2009).

SAFETY SUMMARY

- A boxed warning appears in the lindane labeling for the risk of neurologic toxicity including seizures and deaths. Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies; the AAP no longer recommends lindane as a treatment of head lice (CDC, 2016a; Devore, Schultz, 2015).
- Lindane is contraindicated in patients with crusted (Norwegian) scabies and other skin conditions such as atopic dermatitis or psoriasis that may increase systemic absorption of the drug. Lindane is also contraindicated in premature infants because their scalps are more permeable and individuals with known uncontrolled seizure disorders.
- Malathion lotion is contraindicated for neonates and infants because their scalps are more permeable and may have increased absorption of malathion. Malathion lotion is flammable.
- All topical scabicide and pediculicide products are contraindicated in patients with a sensitivity or allergy to any active or inactive ingredient in the product.
- For the class, adverse events are mostly dermatological in nature.
- Drug interactions for this class are minimal due to the topical application. Consult the prescribing information for lindane regarding a list of drug interactions.

(Clinical Pharmacology, 2017)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Adult Dose	Pediatric Dose	Availability
EURAX (crotamiton)	Scabies: Cream, lotion: prior to application, patients should bathe or shower. A thin layer of cream or lotion should be thoroughly massaged into all skin surfaces from the chin down to the toes including all skin folds and creases. Crotamiton is left on the skin and a second application is advisable 24 hours later. The patient should take a cleansing bath 48 hours after the last application to remove any remaining drug. The CDC does not recommend crotamiton for use in scabies.	Scabies: Use in children is off-label. The use of crotamiton has been described clinically, with the same directions as for adults, in infants and children as young as 2 months of age, but treatment has been reported inferior to permethrin. However, due to treatment failures, other agents appear to be preferred; crotamiton is considered an alternative agent.	Cream: 10% (2 oz/tube) Lotion: 10% (2 oz/bottle, 16 oz/bottle)
Lindane	Lice: Shampoo: apply a sufficient quantity of shampoo onto clean, dry hair; generally one ounce (30 mL) is sufficient, no more than two ounces (60 mL) should be used. Work the shampoo into hair thoroughly and allow to remain on hair for four minutes. Add small quantities of water and massage until a good lather forms. Rinse thoroughly and towel dry briskly. Nits should be removed using a nit comb or tweezers. Retreatment is not recommended.	The use of lindane should be avoided in infants and young children due to a higher incidence of adverse reactions in this age group.	Shampoo: 1% (2 oz/bottle)
NATROBA (spinosad)	Lice: Suspension: apply sufficient amount to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off with warm water. If live lice are seen seven days following the first treatment, a second treatment should be applied.	Lice: Suspension: apply sufficient amount to cover dry scalp, then apply to dry hair. Depending on hair length, apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off with warm water. If live lice are seen seven days following the first treatment, a second treatment should be applied. Approved for use in children six months of age or older.	Topical Suspension: 0.9% (4 oz/bottle)

Drug	Adult Dose	Pediatric Dose	Availability
OVIDE (malathion)	Head lice: Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion.	Head lice: Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion. This should be used in children six years or older.	Lotion: 0.5% (2 oz/bottle)
Permethrin	Lice: Lotion: a sufficient volume (25 to 30 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after initial application. Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Remove cream by washing 8 to 14 hours after application. Repeat dose 7 to 14 days later if living mites are observed.	Lice: Lotion: a sufficient volume (25 to 30 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after initial application. Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Remove cream by washing 8 to 14 hours after application. Repeat dose 7 to 14 days later if living mites are observed. This should be used in children two months or older.	Cream: 5% (2 oz/tube) Lotion (crème rinse): 1% (2 oz/bottle; 1 and 2 bottles per package)
Piperonyl butoxide and pyrethrins	Lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows. Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours.	Lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows. Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours. This should be used in children two years or older.	Shampoo/Solution: 4% piperonyl butoxide/0.33% pyrethrins (each kit)

Drug	Adult Dose	Pediatric Dose	Availability
SKLICE (ivermectin)	Lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water.	Lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water. This should be used in children six months or older.	Lotion: 0.5% (4 oz/tube)
ULESFIA (benzyl alcohol)	Lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days. Dosing is based on length of hair with ½ bottle to 6 bottles required.	Lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days. Dosing is based on length of hair with ½ bottle to 6 bottles required. This should be used in children six months or older.	Lotion: 5% (two 8 ounce bottles per package)

(Clinical Pharmacology, 2017)

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing*
EURAX (crotamiton)	Clinical studies did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.	Not approved for use in pediatric populations.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
Lindane	May be at greater risk for serious neurotoxicity.	Should not be used in very young children or premature infants due to risk of seizures and death. Use with caution in patients who weigh less than ~50 kg and especially in infants.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Enters breast milk; use is contraindicated. Discard milk for at least 24 hours after application.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing*
NATROBA (spinosad)	Clinical studies did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Not excreted into breast milk; use is recommended only if benefits outweigh the risks because it may be absorbed through the skin.
OVIDE (malathion)	No information	FDA-approved for use in children ≥6 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Permethrin	Safety and efficacy in elderly patients have not been established.	FDA-approved for use in children ≥2 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Piperonyl butoxide and pyrethrins	Safety and efficacy in elderly patients have not been established.	FDA-approved for use in children ≥2 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
SKLICE (ivermectin)	Clinical studies did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Following oral administration, it is excreted in human milk in low amounts; this has not been evaluated following topical administration.
ULESFIA (benzyl alcohol)	Safety and efficacy in elderly patients (>60 years) have not been established.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

(Clinical Pharmacology, 2017)

CONCLUSIONS

- There are a number of effective topical scabicide and pediculicide agents available including EURAX (crotamiton), lindane, OVIDE (malathion), NATROBA (spinosad), NIX (permethrin), RID (piperonyl butoxide with pyrethrins), SKLICE (ivermectin) and ULESFIA (benzyl alcohol). Permethrin is recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States (Downs et al, 1999; CDC, 2016a; Devore, Schultz, 2015).
- Topical insecticides exert their pediculicidal and scabicidal effects through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuroexcitation, theoretically lowering the risk of resistance. Ivermectin and spinosad are two newer agents approved for the treatment of head lice. Spinosad is not extensively metabolized, and therefore, it is still present and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application (Villegas et al, 2012). Ivermectin has been approved for one-time use. Permethrin and the combination of pyrethrins and piperonyl butoxide are available over-the-counter (OTC) (CDC, 2016a). Lindane, a well-known older agent, is reserved as second-line therapy and carries a boxed warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should a resistant case occur, or if a patient experiences treatment failure with an OTC product (CDC, 2016a; Devore, Schultz, 2015).
- Limited direct comparisons have been completed with agents in this class. Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (Brandenburg et al, 1986; Bowerman et al, 1987; Taplin et al, 1986a). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (Carson et al, 1988; DiNapoli et al, 1988). Numerous studies have demonstrated a significantly lower cure rate after four weeks with lindane compared to oral ivermectin (Goldust et al, 2013; Madan et al, 2001; Mohebbipour et al, 2013); however one study found no difference at days 15 and 29 following treatments (Chouela et al, 1999). In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin (Meinking et al, 2004; Roberts et al, 2000).
- The newer agents, which include benzyl alcohol, ivermectin and spinosad, have shown cure rates (lice-free at day 14 or 15) of 75 to 76%, 71 to 76% and 84.6 to 86.7%, respectively, although there is limited published literature confirming these results.
- Overall, topical pediculicides are effective in eradicating head lice, but generally do not have any effect on ova (nits). The guidelines from CDC and AAP recommend permethrin or the combination of pyrethrins and piperonyl butoxide for head lice when resistance is not suspected (AAP Red Book, 2012; CDC, 2016a; Devore, Schultz, 2015). Retreatment of head lice usually is recommended because most approved pediculicides are not completely ovicidal. Spinosad and malathion are the only ovicidal medications for the treatment of head lice, but the need for re-treatment has been reported (CDC, 2016a). Lindane is no longer recommended by the AAP for use as treatment of head lice (Devore, Schultz, 2015).
- A comparison of the overall success rates for the topical scabicide products shows 89 to 100% success with permethrin, 65 to 92% with lindane, and 60 to 88% with EURAX. The CDC guidelines recommend permethrin as the drug of choice for the treatment of scabies; lindane is not recommended as a first-line therapy due to its toxicity, and it should be restricted to patients who have failed treatment with or cannot tolerate other medications that pose less risk (CDC, 2016b). For crusted scabies, oral ivermectin should be co-administered with a topical agent.
- The CDC recommends permethrin or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pediculosis pubis (CDC, 2015).

REFERENCES

- Amer M, el-Garib I. Permethrin versus crotamiton and lindane in the treatment of scabies. Int J Dermatol. 1992;31:357-8.
- American Academy of Pediatrics. Red Book: 2012 Report of the Committee on Infectious Diseases. Pickering LK, ed. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
- Bowerman JG, Gomez MP, Austin RD, et al. Comparative study of permethrin 1% creme rinse and lindane shampoo for the treatment of head lice. Pediatr Infect Dis J. 1987;6:252-5.
- Brandenburg K, Deinard AS, DiNapoli J, et al.1% permethrin cream rinse vs. 1% lindane shampoo in treating pediculosis capitis. Am J Dis Child. 1986; 140:894-6.
- Carson DS, Tribble PW, Weart CW. Pyrethrins combined with piperonyl butoxide (RID) vs. 1% permethrin (NIX) in the treatment of head lice. Am J Dis Child. 1988;142:768-9.
- Centers for Disease Control and Prevention. Parasites – Head Lice. August 19, 2016a. Available at: http://www.cdc.gov/parasites/lice/head/treatment.html. Accessed March 9, 2017.
- Centers for Disease Control and Prevention. Parasites – Pubic "Crab" Lice. Updated August 17, 2015. Available at: http://www.cdc.gov/parasites/lice/pubic/treatment.html. Accessed March 9, 2017.
- Centers for Disease Control and Prevention. Parasites – Scabies. September 16, 2016b. Available at: http://www.cdc.gov/parasites/scabies/health_professionals/meds.html. Accessed March 9, 2017.

- Chosidow O. Clinical practices. Scabies. N Engl J Med. 2006; 354:1718.
- Chouela EN, Abeldaño AM, Pellerano G, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. Arch Dermatol. 1999;135:651-5.
- Clinical Pharmacology® [database on the Internet]. Tampa, FL: Elsevier/Gold Standard; 2017. Available at: www.clinicalpharmacology.com. Accessed March 9, 2017.
- Devore CD, Schutze GE. Council on School Health and Committee on Infectious Diseases. Head lice. Pediatrics. 2015 May;135(5):e1355-e1365.
- DiNapoli JB, Austin RD, Englender SJ, et al. Eradication of head lice with a single treatment. Am J Public Health. 1988;78:978-80.
- Downs AM, Stafford KA, Harvey I, et al. Evidence for double resistance to permethrin and malathion in head lice. Br J Dermatol. Sep 1999;141(3):508-11.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 9, 2017.
- EURAX® prescribing information. Ranbaxy; Jacksonville, FL. September 2012.
- Feldmeier H. Pediculosis capitis: new insights into epidemiology, diagnosis and treatment. Eur J Clin Microbiol Infect Dis. 2012;31(9):2105-2110..
- Goldust M, Rezaee E, Raghiafar R. Topical ivermectin versus crotamiton cream 10% for the treatment of scabies. Int J Dermatol. 2014;53(7):904-908.
- Goldust M, Rezaee E, Raghifar R, et al. Ivermectin vs. lindane in the treatment of scabies. Ann Parasitol. 2013;59(1):37-41.
- Haustein UF, Hlawa B. Treatment of scabies with permethrin versus lindane and benzyl benzoate. Acta Derm Venereol. 1989;69:348-51.
- Kalter DC, Sperber J, Rosen T, et al. Treatment of pediculosis pubis. Clinical comparison of efficacy and tolerance of 1% lindane shampoo vs. 1% permethrin creme rinse. Arch Dermatol. 1987;123:1315-9.
- Koch E, Clark JM, Cohen B et al. Management of Head Louse Infestations in the United States-A Literature Review. Pediatr Dermatol. 2016;33(5):466-72.
- Lindane prescribing information. VersaPharm, Inc.; Marietta, GA. June 2011.
- Madan V, Jaskiran K, Gupta U, et al. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. J Dermatol. 2001;28:481-4.
- Meinking TL, Vicaria M, Eyerdam DH, et al. A Randomized, Investigator-Blinded, Time-Ranging Study of the Comparative Efficacy of 0.5% Malathion Gel Versus Ovide® Lotion (0.5% Malathion) or Nix® Crème Rinse (1% Permethrin) Used as Labeled, for the Treatment of Head Lice. Pediatric Dermatology. 2007; 24(4):405-11.
- Meinking TL, Vicaria M, Eyerdam DH, et al. Efficacy of a reduced application time of Ovide lotion (malathion) compared to Nix crème rinse (1% permethrin) for the treatment of head lice. Pediatric Dermatology. 2004; 21(6);670-4.
- Meinking TL, Villar ME, Vicaria M, et al. The clinical trials supporting benzyl alcohol lotion 5% (Ulesfia): a safe and effective topical treatment for head lice (pediculosis humanus capitis). Pediatr Dermatol. 2010 Jan-Feb;27(1):19-24.
- Mohebbipour A, Saleh P, Goldust M, et al. Comparison of oral ivermectin vs. lindane lotion 1% for the treatment of scabies. Clin Exp Dermatol. 2013 Oct;38(7):719-23.
- NATROBA® prescribing information. ParaPro LLC; Carmel, IN. December 2014.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 9, 2017.
- OVIDE® prescribing information. Taro Pharmaceuticals U.S.A., Inc.; Hawthorne, NY. September 2013.
- Pariser DM, Meinking TL, Bell M, et al. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov; 367(18):1687-93.
- Roberts RJ, Casey D, Morgan DA, et al. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomized controlled trial. Lancet. 2000;356:540-4.
- Roos TC, Alam M, Roos S, et al. Pharmacotherapy of ectoparasitic infections. Drugs. 2001;61:1067-88.
- Schultz MW, Gomez M, Hansen RC, et al. Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. Arch Dermatol. 1990;126:167-70.
- SKLICE® prescribing information. Sanofi Pasteur Inc.; Swiftwater, PA. January 2016.
- Stough D, Shellabarger MS, Quiring J, et al. Efficacy and safety and spinosad and permethrin crème rinses for pediculosis capitis (head lice). Pediatrics. 2009;124:389e-95e.
- Taplin D, Meinking TL, Castillero PM, et al. Permethrin 1% creme rinse for the treatment of Pediculus humanus capitis infestation. Pediatr Dermatol. 1986[a];3:344-8.
- Taplin D, Meinking TL, Chen JA., et al. Comparison of crotamiton 10% cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. Pediatr Dermatol. 1990;7:67-73.
- Taplin D, Meinking TL, Porcelain SL, et al. Permethrin 5% dermal cream: a new treatment for scabies. J Am Acad Dermatol. 1986[b];15:995-1001.
- The Medical Letter. Drugs for Head Lice. The Medical Letter. November 2016: 58(1508):150-152.
- ULESFIA® prescribing information. Shionogi Pharma Inc.; Florham Park, NJ. June 2015.
- Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. J Am Acad Dermatol. 2000; 42(2 Pt 1):236-40.
- Villegas SC, Breitzka RL. Head lice and the use of spinosad. Clin Ther. 2012 Jan;34(1):14-23.
- Wendel K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. Clin Infect Dis. 2002;35(Suppl 2):S146-51.
- Zargari O, Golchai J, Sobhani A, et al. Comparison of the efficacy of topical 1% lindane vs. 5% permethrin in scabies: A randomized, double-blind study. Indian J Dermatol Venereol Leprol. 2006;72;33-6.

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Therapeutic Class Overview
Proton Pump Inhibitors

INTRODUCTION

- The proton pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available. Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K^+) for hydrogen ions (H^+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid (Wolfe et al, 2000). Approximately 70% to 80% of the proton pumps will be active following a meal (Welage, 2003). As a result, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in three to four days (Welage, 2003; Wolfe et al, 2000).
- There are currently six PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (DEXILANT®, DEXILANT SOLUTAB®, esomeprazole (NEXIUM®, NEXIUM IV®, NEXIUM® 24HR), esomeprazole strontium, lansoprazole (PREVACID®, PREVACID SOLUTAB®, PREVACID® 24HR), omeprazole (PRILOSEC®, PRILOSEC OTC®, ZEGERID®, ZEGERID OTC®), pantoprazole (PROTONIX®, PROTONIX IV®), and rabeprazole (ACIPHEX®, ACIPHEX® SPRINKLE™), of which certain formulations of rabeprazole, esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically. In addition, lansoprazole, esomeprazole magnesium, omeprazole, and omeprazole with sodium bicarbonate are available over-the-counter (OTC). Currently available PPI combination products include aspirin/omeprazole (YOSPRALA®) and naproxen/esomeprazole (VIMOVO®); these combination products are outside the scope of this overview and will not be reviewed.
- In August 2013, esomeprazole strontium was Food and Drug Administration (FDA)-approved without a proprietary name. Its approval was based on bioequivalence of esomeprazole strontium 24.65 mg and 49.3 mg delayed-release capsules to esomeprazole magnesium 20 and 40 mg delayed-release capsules, respectively. Shortly after its approval, the manufacturer made an authorized generic available by the same name. Both strengths of this product were discontinued for several months during 2015-2016, but reappeared on the market with a different manufacturer in September 2016.
- All of the PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomer of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small and the clinical significance has not been established. When administered in equivalent dosages, the PPIs have generally demonstrated comparable efficacy to one another (Dean, 2010).
  - Dexlansoprazole, the enantiomer of lansoprazole and the newest agent in the class, is the first PPI with a dual delayed-release formulation designed to provide two separate releases of medication. It contains two types of enteric-coated granules resulting in a concentration-time profile with two distinct peaks: the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. In addition, it can be taken regardless of meals (DEXILANT prescribing information, 2016).
  - DEXILANT SOLUTAB, an orally disintegrating, delayed release tablet formulation of dexlansoprazole, was approved in January 2016; however, the formulation is currently not available.
- In general, all PPIs are FDA-approved for the treatment of gastroesophageal reflux disease (GERD) and for the healing and maintenance of erosive esophagitis. Some of the agents also have approval for the treatment of peptic ulcer disease, the treatment of pathological hypersecretory conditions, and *Helicobacter pylori (H. pylori)* eradication as part of combination therapy with antibiotics.
- Current national and international consensus guidelines recognize the PPIs as first-line therapy for the management of dyspepsia, GERD, peptic ulcer disease, and eradication of *H. pylori.* In addition, these agents have a role in the management of Barrett's esophagus. Currently available guidelines do not give preference to one PPI over another (American Gastroenterological Association, 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Koletzko et al, 2011; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2012; Shaheen et al, 2016; Talley et al, 2005; Talley, Vakil et al, 2005).

- The agents included in this review are listed alphabetically by brand name in Table 1. Since there are multiple branded agents that contain the same generic component(s) the remaining tables in the review are organized alphabetically by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ACIPHEX (rabeprazole) delayed-release tablet	various generic	08/19/1999	√
ACIPHEX SPRINKLE (rabeprazole) delayed-release capsule	Eisai Inc.	03/26/2013	-
DEXILANT (dexlansoprazole) delayed-release capsule	Takeda Pharms	01/30/2009	-
DEXILANT SOLUTAB (dexlansoprazole) delayed-release orally disintegrating, tablet	Takeda Pharms	01/26/2016	-
esomeprazole strontium, delayed-release capsule	R2 Pharma LLC	08/06/2013	√
NEXIUM (esomeprazole magnesium) delayed-release capsule	various generic	02/20/2001	√
NEXIUM (esomeprazole magnesium) powder for delayed-release oral suspension	AstraZeneca	10/20/2006	-
NEXIUM IV (esomeprazole sodium) injection	various generic	03/31/2005	√
NEXIUM 24HR* (esomeprazole magnesium) delayed-release capsules	Pfizer Consumer Healthcare	03/28/2014	-
NEXIUM 24HR* (esomeprazole magnesium) delayed-release tablets	Pfizer Consumer Healthcare	11/23/2015	-
PREVACID (lansoprazole) delayed-release capsule	various generic	05/10/1995	√
PREVACID 24HR* (lansoprazole) delayed-release capsule	various generic	05/18/2009	√
PREVACID SOLUTAB (lansoprazole) delayed-release orally disintegrating tablet	Takeda Pharms USA	08/30/2002	-
PRILOSEC (omeprazole magnesium) delayed-release capsule	various generic	09/14/1989	√
PRILOSEC (omeprazole magnesium) powder for delayed-release oral suspension	AstraZeneca	03/20/2008	-
PRILOSEC OTC* (omeprazole magnesium) delayed-release tablet	various generic	06/20/2003	√
PROTONIX (pantoprazole) delayed-release tablet	various generic	02/02/2000	√
PROTONIX (pantoprazole) powder for delayed-release oral suspension	Wyeth Pharms Inc.	11/14/2007	-
PROTONIX IV (pantoprazole) injection, powder for solution	various generic	03/22/2001	√
ZEGERID (omeprazole with sodium bicarbonate) capsule	various generic	02/27/2006	√
ZEGERID (omeprazole with sodium bicarbonate) powder for oral suspension	various generic	06/15/2004	√
ZEGERID OTC* (omeprazole with sodium bicarbonate) capsule	various generic	12/01/2009	√
ZEGERID OTC* (omeprazole with sodium bicarbonate) powder for suspension	Bayer Healthcare	06/17/2013	-

*Available OTC.

(DRUGS@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Dexlansoprazole	Esomeprazole magnesium and strontium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ Sodium bicarbonate	Pantoprazole	Rabeprazole
GERD[e]								
Maintaining healing of erosive esophagitis	√	√		√	√	√	√	√
Treatment of erosive esophagitis	√[d]	√	√	√	√	√	√[c]	√
Treatment of symptomatic GERD	√	√		√	√	√		√
Peptic Ulcer Disease								
Healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer				√				
H. pylori eradication to reduce the risk of duodenal ulcer recurrence		√[b]		√[b]	√[b]			√[b]
Maintenance of healing duodenal ulcers				√				
Risk reduction of NSAID-associated gastric ulcer		√		√				
Treatment of active, benign gastric ulcer				√	√	√		
Treatment of active duodenal ulcers				√	√	√		√
Other								
Risk reduction of upper gastrointestinal bleeding in critically ill patients						√		
Treatment of frequent heartburn for up to 14 days		√ (NEXIUM 24HR)		√ (PREVACID 24HR)	√ (PRILOSEC OTC)	√ (ZEGERID OTC)		
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome		√		√	√		√[a]	√
Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults			√					

a Intravenous and oral formulation.

b As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).

c Oral formulations indicated for the short-term treatment of erosive esophagitis associated with GERD; intravenous formulation indicated for the short-term treatment of adult patients with GERD associated with a history of erosive esophagitis.
d DEXILANT SOLUTAB is not approved for healing of erosive esophagitis.
e Esomeprazole magnesium/sodium, lansoprazole, omeprazole, pantoprazole, and rabeprazole are approved for pediatric patients. Dexlansoprazole is indicated for patients 12 years of age or older. Esomeprazole strontium and omeprazole/sodium bicarbonate are approved for adult patients.

(Prescribing information: ACIPHEX, 2016; ACIPHEX SPRINKLE, 2016; DEXILANT, 2016; DEXILANT SOLUTAB, 2016; esomeprazole strontium, 2016; NEXIUM, 2016; NEXIUM IV, 2016; NEXIUM 24HR, 2016; PREVACID, 2016; PREVACID 24HR, 2016; PRILOSEC, 2016; PRILOSEC OTC, 2016; PROTONIX, 2017; PROTONIX IV, 2016; ZEGERID, 2016; ZEGERID OTC, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials consistently demonstrate that the PPIs are highly effective in treating, providing symptom relief, and preventing relapse in gastric acid disorders such as GERD and peptic ulcer disease (Armstrong et al, 2004; Bardhan et al, 2001; Bazzoli et al, 1998; Caro et al, 2001; Castell et al, 2002; Castell et al, 2005; Chan et al, 2010; Chey et al, 2003; Choi et al, 2007; Conrad et al, 2005; Delchier et al, 2000; Devault et al, 2006; Edwards et al, 2001; Fass et al, 2009; Fass et al, 2011; Fass et al, 2012; Felga et al, 2010; Fennerty et al, 2005; Fujimoto et al, 2011; Gisbert et al, 2003; Gisbert et al, 2004; Gisbert, Khorrami et al, 2004; Goh et al, 2007; Haddad et al, 2013; Howden et al, 2002; Howden et al, 2009; Hsu et al, 2005; Kahrilas et al, 2000; Katz et al, 2007; Khorrami et al, 2004; Kinoshita et al, 2011; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Laine et al, 2011; Lauritsen et al, 2003; Lightdale et al, 2006; McNicholl et al, 2012; Metz et al, 2009; Mönnikes et al, 2012; Pace et al, 2005; Pilotto et al, 2007; Pouchain et al, 2012; Ramdani et al, 2002; Regula et al, 2006; Richter et al, 2001; Richter, Kahrilas, Sontag et al, 2001; Scheiman et al, 2011; Schmitt et al, 2006; Scholten et al, 2003; Sharma et al, 2001; Sharma et al, 2009; Sugano et al, 2011; Tsai et al, 2004; Ulmer et al, 2003; van Pinxteren et al, 2010; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007).
- The safety and efficacy of esomeprazole strontium have been established based on adequate and well-controlled adult studies of esomeprazole magnesium in the healing and maintenance of erosive esophagitis, symptomatic GERD, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.
- A number of studies have compared the various PPIs to one another. While some differences have been reported, the magnitude of differences has been small and of uncertain clinical importance. In particular, the degree to which any of the reported differences would justify the selection of one versus another PPI, particularly when considering cost-effectiveness, is unclear (Wolfe, 2017).

GERD

- In meta-analyses and direct comparator trials, lansoprazole, omeprazole, pantoprazole, and rabeprazole have demonstrated comparable healing rates, maintenance of healing, and/or symptomatic relief of GERD (Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001). Furthermore, Richter et al reported that lansoprazole produced a significantly quicker and greater symptomatic relief of GERD compared to omeprazole; however, the absolute differences between the two treatments were small and the clinical impact of the difference was not measured within the clinical trial (Richter, Kahrilas, Sontag et al, 2001).
- The results of several meta-analyses and clinical trials demonstrate that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole at four and eight weeks (Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Richter et al, 2001). Subgroup analyses of two trials note higher healing rates with esomeprazole in patients with more severe disease (Labenz et al, 2005[a]; Schmitt et al, 2006).
- Close analyses of all of these trials demonstrate that the overall differences between the various PPI agents were generally small and the clinical significance is not clear. In addition, results of these trials have not been consistently demonstrated in other clinical trials, particularly in those evaluating lansoprazole and pantoprazole (Armstrong et al, 2004; Chey et al, 2003; Goh et al, 2007; Howden et al, 2002; Lightdale et al, 2006; Scholten et al, 2003).

Peptic Ulcer Diseases

- Meta-analyses and head-to-head trials comparing various PPIs for the treatment of peptic ulcer disease with *H. pylori* demonstrate comparable rates of eradication when paired with comparable antibiotic regimens (Bazzoli et al, 1998; Choi et al, 2007; Gisbert et al, 2003; Gisbert et al, 2004; Gisbert, Khorrami et al, 2004; Ulmer et al, 2003; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007).
- Results from two meta-analyses suggest that both esomeprazole- and rabeprazole-based *H. pylori* regimens are more effective with regard to eradication rates compared to traditional PPI-based regimens (lansoprazole, omeprazole, and pantoprazole) (McNicholl et al, 2012; Xin et al, 2016).

Current Guidelines

- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. None of the treatment guidelines recommend one PPI over another or one formulation of a PPI over another (American Gastroenterological Association, 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Koletzko et

al, 2011; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2012; Shaheen et al, 2016; Talley et al, 2005; Talley, Vakil et al, 2005).

- According to the American Gastroenterological Association (AGA) medical position statement on the management of GERD (2008) and the American College of Gastroenterology (ACG) guideline for the diagnosis and management of GERD (2013), PPIs are considered the drug of choice in the treatment of GERD with H_2-receptor antagonists as an alternative agent that can be used for maintenance of GERD symptoms without erosive disease (AGA Institute Medical Position Panel, 2008; Katz et al, 2013). The ACG medical position notes that there are no major differences between the different PPIs (Katz et al, 2013).
- According to joint recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (2009), PPIs are recommended in older children or adolescents with chronic heartburn for four weeks in conjunction with lifestyle modifications and in infants or children with reflux esophagitis as initial treatment in conjunction with lifestyle modifications. Patients with asthma and heartburn should also be treated for heartburn (Vandenplas et al, 2009).
- According to the ACG guideline for prevention of NSAID-related ulcer complications (2009), misoprostol or high-dose PPI treatment is recommended as co-therapy with anti-inflammatory analgesics in certain patients with high- and moderate-NSAID gastrointestinal risk. In patients who require both anti-inflammatory analgesics and low-dose aspirin, naproxen with either misoprostol or a PPI are also recommended (Lanza et al, 2009).
- According to the ACG guideline on the management of *H. pylori* infection (2017), there are many first-line options for *H. pylori* treatment; a regimen should be based on patient allergies, previous macrolide exposure, and known *H. pylori* resistance rates. A PPI, clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) regimen for 14 days is recommended where *H. pylori* clarithromycin resistance is known to be < 15%. Alternately, bismuth quadruple therapy, consisting of a PPI, bismuth, tetracycline, and a nitroimidazole (metronidazole or tinidazole) for ten to 14 days should be considered as a first-line therapy option for areas of high clarithromycin resistance (Chey et al, 2017).
- High-dose PPIs are often used as primary long-term therapy in Zollinger-Ellison syndrome. PPIs are considered generally safe, even at high doses, and have demonstrated superior acid suppression, healing rates, and symptom relief compared with other antisecretory therapies (Bergsland, 2016; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] Web site).
- A 2015 clinical guideline by the ACG also recognized the use of PPIs in the management of Barrett's Esophagus; long-term PPI use will likely produce a net benefit for these patients (Freedberg et al, 2017; Shaheen et al, 2016).

SAFETY SUMMARY

- In general, the PPIs are well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events.
- Long-term use of PPIs for five or more years has been associated with an increase in hip fractures (Targownik et al, 2008). When administered for seven or more years, PPIs have been associated with a significantly increased risk of an osteoporosis-related fracture. At this time, there is inadequate evidence to mandate bone density studies and calcium supplementation in patients receiving chronic PPI therapy (Freedberg et al, 2017; Kahrilas et al, 2008). Additional data are needed to determine the value of osteoporotic medications in patients receiving long-term PPI therapy (Targownik et al, 2008). The 2013 guidelines for the diagnosis and management of GERD recommend continuation of PPI therapy unless additional risk factors for osteoporosis exist (Katz et al, 2013).
- Contraindications of the PPIs include hypersensitivity to any component of their formulations. ACIPHEX, ACIPHEX SPRINKLE, DEXILANT, DEXILANT SOLUTAB, and PRILOSEC are also contraindicated in patients receiving rilpivirine-containing products.
- Warnings and precautions with the use of PPIs include acute interstitial nephritis, cyanocobalamin deficiency, *Clostridium difficile*-associated diarrhea, bone fractures, and hypomagnesemia. Concomitant use with clopidogrel, St. John's Wort, rifampin, high-dose methotrexate, and some antiretroviral medications (e.g., protease inhibitors such as atazanavir and nelfinavir) should be avoided. False positive results for diagnostic investigations of neuroendrocrine tumors may occur due to an increase in serum chromogranin A (CgA) levels. Cutaneous and systemic lupus erythematosus have been reported in patients taking PPIs; new onset events and exacerbations of existing autoimmune disease have occurred. Finally, symptomatic response to PPI therapy does not preclude the presence of gastric malignancy.
- The concomitant use of PPIs with thienopyridines such as clopidogrel was addressed in a consensus guideline from the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association, which recommended PPI therapy be continued unless additional risk factors for cardiovascular disease exist (Abraham et al, 2010). A systematic review exploring the use of PPIs in combination with dual antiplatelet therapy that included clopidogrel showed inconclusive results for causing cardiovascular events while another

systematic review showed an increase in cardiovascular events with pantoprazole, lansoprazole, and esomeprazole but not with omeprazole (Melloni et al, 2015; Sherwood et al, 2015). In a large, longitudinal, observational study of patients discharged after acute myocardial infarction treated with percutaneous coronary intervention, the use of clopidogrel or prasugrel in combination with a PPI was associated with statistically significantly more cardiovascular events than patients not discharged on a PPI (adjusted hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.21 to 1.58). However, the authors noted that patients prescribed a concurrent PPI were more likely to be older and have more complex comorbidity profiles (Jackson et al, 2016).

- Recent research has demonstrated an association with PPIs and cardiovascular, renal, and neurological morbidity. PPI use interferes with acid production in endothelial lysosomes, leading to oxidative stress and accelerated cell death, and may contribute to the pathogenesis of the aforementioned morbidities (Yepuri et al, 2016).
  - A retrospective study using a data mining strategy identified 2.9 million patients in the general population taking PPIs for GERD. Data showed that GERD patients exposed to PPIs had a 1.16 fold increased association with myocardial infarction and a two-fold increased association with cardiovascular mortality. H_2-receptor antagonists used for GERD were not associated with any increased cardiovascular risk (Shah et al, 2015).
  - In a large cohort study, 144,032 incident users of either PPIs or H_2-antagonists were followed for five years. Patients using PPIs had an increased risk of incident chronic kidney disease (HR, 1.26; 95% CI, 1.2 to 1.33) and increased risk of estimated glomerular filtration rate decline and end-stage renal disease as compared to H_2-antagonist users (Xie et al, 2017). Similar patterns were identified in another large population-based cohort study; twice-daily PPI dosing was associated with a higher risk than once-daily dosing (Lazarus et al, 2016).
  - A prospective cohort using observational data from 73,679 patients ≥ 75 years and dementia-free at baseline were analyzed. Patients on PPIs (N = 2950) had a significantly increased risk of dementia than patients not on PPIs (HR, 1.44; 95% CI, 1.36 to 1.52, P < 0.001) (Gomm et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Dexlansoprazole	Delayed-release capsule: 30 mg 60 mg SoluTab delayed-release orally disintegrating tablets: 30 mg **Note:** Two 30 mg DEXILANT SoluTabs are not interchangeable with one 60 mg DEXILANT capsule. Both formulations are indicated for patients ≥ 12 years of age.	Treatment of symptomatic, non-erosive GERD: 30 mg daily for four weeks Treatment of erosive esophagitis: 60 mg daily for up to eight weeks Maintenance of healing of erosive esophagitis: 30 mg daily[a]	Delayed-release capsules can be taken without regard to food. Delayed-release capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Delayed-release capsules can be opened and contents mixed in 20 mL of water for administration in an oral syringe for immediate consumption. Refill the oral syringe with 10 mL of water twice to ensure all of the contents are delivered. Delayed-release capsules can be opened with contents mixed in 20 mL of water and withdrawn in a catheter-tip syringe and administered by nasogastric tube. Refill the syringe with 10 mL of water twice to flush the tube. SoluTabs must be taken at least 30 minutes before a meal. SoluTabs should not be broken, chewed, or cut. Tablets should be placed on the tongue, allowed to disintegrate, and the microgranules

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			swallowed without water. SoluTabs may also be swallowed whole with water.
Esomeprazole magnesium	Delayed-release capsule: 20 mg 40 mg Delayed-release suspension (unit-dose packets): 2.5 mg 5 mg 10 mg 20 mg 40 mg Delayed-release capsule (OTC): 22.3 mg Delayed-release tablet (OTC): 22.3 mg	Treatment of symptomatic GERD (≥ 12 years of age): 20 mg daily for four weeks[b] *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 40 mg daily for ten days[c] Treatment of erosive esophagitis (≥ 12 years of age): 20 mg or 40 mg daily for four to eight weeks Maintenance of healing of erosive esophagitis: 20 mg daily[a] Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: 40 mg twice daily[d] Risk reduction of NSAID-associated gastric ulcer: 20 or 40 mg daily for up to six months[a] Treatment of frequent heartburn (OTC): 22.3 mg daily for 14 days[i] Treatment of symptomatic GERD, short-term (1 to 11 years of age)[e]: 10 mg daily for up to eight weeks Treatment of erosive esophagitis (1 to 11 years of age)[e]: Weight-based dosing Patients weighing < 20 kg: 10 mg once daily for eight weeks Patients weighing ≥ 20 kg: 10 mg or 20 mg once daily for eight weeks Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age)[e]: Weight-based dosing Patients weighing 3 kg to 5 kg: 2.5 mg once daily for up to six	Should be taken at least one hour before meals. Capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Contents can also be emptied into 60 mL catheter tipped syringe and shaken with 50 mL water for administration via nasogastric tube. Packets for delayed-release suspension should be emptied into water (5 mL for 2.5 mg or 5 mg; 15 mL for 10 mg, 20 mg, or 40 mg), stirred, left for two to three minutes to thicken, and drank within 30 minutes. Can also be emptied into catheter-tipped syringe for administration via nasogastric tube.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		weeks Patients weighing > 5 kg to 7.5 kg: 5 mg once daily for up to six weeks Patients weighing > 7.5 kg to 12 kg: 10 mg for up to six weeks	
Esomeprazole sodium	Powder for injection: 20 mg 40 mg	Treatment of symptomatic GERD with erosive esophagitis (Adults)[f]: 20 mg or 40 mg once daily by IV injection (no less than 3 minutes) or IV infusion (10 to 30 minutes) Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults: 80 mg IV infusion over 30 minutes followed by a continuous infusion of 8 mg/h over three days (72 hours) Treatment of symptomatic GERD with erosive esophagitis (1 to 17 years of age)[f]: Weight-based dosing Patients weighing < 55 kg: 10 mg once daily Patients weighing ≥ 55 kg: 20 mg once daily Treatment of symptomatic GERD with erosive esophagitis (1 month to < 1 year)[f]: Weight-based dosing 0.5 mg/kg once daily	Should be discontinued in favor of oral therapy as soon as oral therapy is possible. No refrigeration required. Reconstituted with 0.9% sodium chloride (to be administered within 12 hours), Lactated Ringer's (within 12 hours), or 5% dextrose (within six hours). Loading dose and continuous infusion prepared by reconstitution of two 40 mg vials with 5 mL 0.9% sodium chloride each, then further diluted in 100 mL of 0.9% sodium chloride.
Esomeprazole strontium	Delayed-release capsule: 24.65 mg (equivalent to 20 mg esomeprazole) 49.3 mg (equivalent to 40 mg esomeprazole)	Treatment of erosive esophagitis in adults: 24.65 or 49.3 mg once daily for four to eight weeks Maintenance of healing of erosive esophagitis in adults: 24.65 mg once daily[a] Treatment of symptomatic GERD in adults: 24.65 mg once daily for four weeks Risk reduction of NSAID-associated gastric ulcer in adults: 24.65 or 49.3 mg once daily[a] *H. pylori* eradication (triple	Should be taken at least one hour before meals. Capsule can be swallowed whole. Do not chew or crush capsule. Capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Do not chew or crush granules. Contents can also be emptied into 60 mL catheter tipped syringe and shaken with 50 mL water for administration via nasogastric tube.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		therapy) in adults: 49.3 mg once daily for ten days[k] Pathological hypersecretory conditions in adults: 49.3 mg twice daily[d]	
Lansoprazole	Delayed-release capsule: 15 mg 30 mg Delayed-release orally disintegrating tablet: 15 mg 30 mg Delayed-release capsule (OTC): 15 mg	Treatment of symptomatic GERD and heartburn (adults): 15 mg daily for up to eight weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 30 mg twice daily for 10 or 14 days[c] or 30 mg three times daily for 14 days[g] Treatment of active duodenal ulcers: 15 mg daily for four weeks Treatment of erosive esophagitis: 30 mg daily for up to eight weeks[h] Treatment of active, benign gastric ulcer: 30 mg daily up to eight weeks Healing of NSAID associated gastric ulcer: 30 mg daily for eight weeks Maintenance of healing duodenal ulcers: 15 mg daily Maintenance of healing of erosive esophagitis: 15 mg daily[m] Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: 60 mg daily[d] Risk reduction of NSAID associated gastric ulcer: 15 mg daily up to 12 weeks Treatment of symptomatic GERD and erosive esophagitis (1 to 11 years of age): Weight-based dosing	Should be taken before eating and swallowed whole. Capsules (non-OTC) can be opened and contents sprinkled into applesauce, Ensure pudding, cottage cheese, yogurt, or strained pears. May be mixed in 60 mL apple juice, orange juice, or tomato juice for immediate consumption. Contents can also be mixed into 40 mL apple juice for administration via nasogastric tube, flushing with additional juice. Orally disintegrating tablets should be placed on tongue, allowed to disintegrate, and swallowed. Orally disintegrating tablets may also be mixed with water (4 mL for 15 mg tablet or 10 mL for 10 mg tablet) in an oral syringe and gently shaken for oral or nasogastric tube administration.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Patients weighing ≤ 30 kg: 15 mg daily for up to 12 weeks Patients weighing > 30 kg: 30 mg daily for up to 12 weeks Treatment of symptomatic nonerosive GERD (12 to 17 years of age): 15 mg once daily for up to eight weeks Treatment of symptomatic GERD with erosive esophagitis (12 to 17 years of age): 30 mg once daily for up to eight weeks Treatment of frequent heartburn (OTC): 15 mg daily for 14 days[i]	
Omeprazole magnesium	Delayed-release capsule: 10 mg 20 mg 40 mg Delayed-release suspension (unit-dose packet): 2.5 mg 10 mg Delayed-release tablet (OTC): 20 mg	Treatment of symptomatic GERD and heartburn (adults): 20 mg daily for four weeks Treatment of symptomatic GERD and erosive esophagitis due to acid-mediated GERD (1 to 16 years of age)[j]: Weight-based dosing Patients weighing 5 kg to < 10 kg: 5 mg daily Patients weighing 10 kg to < 20 kg: 10 mg daily Patients weighing ≥ 20 kg: 20 mg daily *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (adults): 20 mg twice daily for 10 days[k] or 40 mg daily for 14 days[l] Treatment of active duodenal ulcers (adults): 20 mg daily for four weeks; some patients may require an additional four weeks Treatment of erosive esophagitis due to acid-mediated GERD (adults): 20 mg daily for four to eight weeks Treatment of erosive esophagitis due to acid-mediated GERD	Should be taken before eating. Capsules can be opened and contents sprinkled into applesauce, Ensure, pudding, cottage cheese, yogurt, strained pears, apple juice, orange juice, or tomato juice for immediate consumption. Unit-dose packets should be emptied into water (5 mL for 2.5 mg or 15 mL for 10 mg), stirred, left for two to three minutes to thicken, and drank within 30 minutes. Can also be emptied into catheter-tipped syringe for administration via nasogastric tube.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		(1 month to < 1 year of age): Weight-based dosing Patients weighing 3 kg to < 5 kg: 2.5 mg daily for up to six weeks Patients weighing 5 kg to < 10 kg: 5 mg daily for up to six weeks Patients weighing ≥ 10 kg: 10 mg daily for up to six weeks Treatment of active, benign gastric ulcer (adults): 40 mg daily for four to eight weeks Maintenance of healing of erosive esophagitis due to acid-mediated GERD (adults): 20 mg daily[m] Maintenance of healing of erosive esophagitis due to acid-mediated GERD (1 to 16 years of age): Weight-based dosing Patients weighing 5 to < 10 kg: 5 mg daily Patients weighing 10 to < 20 kg: 10 mg daily Patients weighing ≥ 20 kg: 20 mg once daily Note: Controlled studies do not extend beyond 12 months. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (adults): 60 mg daily[d] Treatment of frequent heartburn (OTC): 20 mg daily for 14 days[i]	
Omeprazole/ sodium bicarbonate	Capsule: 20 mg/1,100 mg 40 mg/1,100 mg Powder for oral suspension (unit-dose packet): 20 mg/1,680 mg 40 mg/1,680 mg Capsule (OTC): 20 mg/1,100 mg	Treatment of symptomatic GERD (with no esophageal erosions): 20 mg daily for four weeks Treatment of active duodenal ulcers: 20 mg daily for four weeks; some patients may require an additional four weeks Treatment of erosive esophagitis:	Should be taken on an empty stomach at least one hour before a meal. Capsules should be swallowed intact with only water and should never be opened. Due to sodium bicarbonate content, one 40 mg unit (capsule or powder packet) is not equivalent to two 20 mg units; therefore, two 20 mg units should not be substituted for one 40 mg unit.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
	Note: all formulations are indicated for adults only. Their safety and effectiveness in pediatric patients < 18 years of age have not been established.	20 mg daily for four to eight weeks Treatment of active, benign gastric ulcer: 40 mg daily for four to eight weeks[m] Maintenance of healing of erosive esophagitis: 20 mg daily[m] Risk reduction of upper gastrointestinal bleeding in critically ill patients: Powder for oral suspension (40 mg/1,680 mg): initial, 40 mg; followed by 40 mg six to eight hours later and 40 mg daily thereafter for 14 days[m] Treatment of frequent heartburn (OTC): 20 mg/1,100 daily for 14 days	Packets for delayed-release oral suspension should be emptied into a small cup with one to two tablespoons of water, stirred well, and drank immediately. Can also be constituted with 20 mL water in an appropriate-sized syringe for administration via nasogastric or orogastric tube. Patients receiving continuous nasogastric or orogastric tube feedings should have these feedings suspended three hours before and one hour after omeprazole/ sodium bicarbonate administration.
Pantoprazole	Delayed-release suspension (unit-dose packet): 40 mg Delayed-release tablet: 20 mg 40 mg Powder for injection: 40 mg	Treatment of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg daily for up to eight weeks Maintenance of healing of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg daily[m] Treatment of GERD associated with a history of erosive esophagitis: Powder for injection: 40 mg daily for seven to ten days Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release suspension, delayed-release tablet: 40 mg twice daily[d] Powder for injection: 80 mg twice daily[n] Treatment of erosive esophagitis (≥ 5 years of age): Delayed-release suspension,	Powder for injection should be discontinued in favor of oral therapy as soon as oral therapy is possible. Tablets can be taken with or without food and should be swallowed whole. Delayed-release oral suspension should only be administered approximately 30 minutes prior to a meal in one teaspoonful of applesauce (eat within 10 minutes) or apple juice (drink immediately). Can also be mixed with 10 mL apple juice in a catheter-tipped 60 mL syringe for administration via nasogastric tube or gastrostomy tube. No refrigeration required. Can be reconstituted for two-minute or fifteen-minute infusion: Two-minute infusion is reconstituted with 10 mL of 0.9% sodium chloride to 4 mg/mL and must be used within 24 hours. Fifteen-minute infusion is reconstituted with 10 mL of 0.9% sodium chloride (stored up to six hours) and further

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		delayed-release tablet: Weight based dosing Patients weighing ≥ 15 kg to < 40 kg: 20 mg daily for eight weeks Patients weighing ≥ 40 kg: 40 mg daily for eight weeks	diluted with 100 mL of 0.9% sodium chloride, Lactated Ringer's, or 5% dextrose to a final concentration of 0.4 (GERD) or 0.8 mg/mL (pathological hypersecretory conditions). Final fifteen-minute infusion mixture must be used within 24 hours.
Rabeprazole	Delayed-release tablet: 20 mg Sprinkle delayed-release capsule: 5 and 10 mg	Treatment of symptomatic GERD: 20 mg daily for up to four weeks[b] *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 20 mg twice daily for seven days[c] Healing of duodenal ulcers: 20 mg daily after the morning meal for up to four weeks Healing of erosive or ulcerative GERD: 20 mg daily for four to eight weeks Maintenance of healing of erosive or ulcerative GERD: 20 mg daily[m] Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: 60 mg daily[d] Treatment of symptomatic GERD in adolescent patients ≥ 12 years of age: 20 mg daily for up to eight weeks Treatment of GERD in pediatric patients 1 to 11 years of age (ACIPHEX SPRINKLE): Weight-based dosing Patients weighing < 15 kg: 5 mg once daily for up to 12 weeks with an option to increase to 10 mg if inadequate response Patients weighing ≥ 15 kg: 10 mg once daily for up to 12 weeks	Take 30 minutes before a meal. For *H. pylori* regimen, take with morning and evening meals. Swallow tablets whole; do not chew, crush, or split. Contents of the ACIPHEX SPRINKLE capsules may be sprinkled on a spoonful of soft food or liquid, take the full dose within 15 minutes.

GERD=gastroesophageal reflux disease; IV=intravenous; NSAID=nonsteroidal antiinflammatory drug; OTC=over-the-counter
a For dexlansoprazole, controlled studies did not extend beyond six months in adults and 16 weeks in patients 12 to 17 years of age. For esomeprazole magnesium, controlled studies did not extend beyond six months.
b If symptoms do not resolve completely after four weeks, an additional four weeks of treatment may be considered.
c As triple therapy with amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily.

d Doses in patients with pathological hypersecretory conditions vary with the individual patient. Dosage regimens should be adjusted to patient needs and continued for as long as clinically indicated.
e For 1 to 11 year olds, doses >1 mg/kg/day have not been studied. For patients 1 month to <1 year old, doses >1.33 mg/kg/day have not been studied.
f Indicated for the short-term treatment of GERD with erosive esophagitis as an alternative to oral therapy when oral esomeprazole magnesium is not possible or appropriate.
g As combination therapy with amoxicillin 1,000 mg three times daily.
h For patients who do not heal with lansoprazole for eight weeks (5 to 10%), it may be helpful to give an additional eight weeks of treatment. If there is a recurrence of erosive esophagitis, an additional eight-week course of lansoprazole may be considered.
i A 14-day course every four months may be considered if required.
j The treatment of symptomatic GERD in patients 1 to 16 years of age is once daily for up to four weeks. The treatment of erosive esophagitis due to acid-mediated GERD in patients 1 to 16 years of age is once daily for four to eight weeks. The efficacy of omeprazole used for longer than eight weeks in patients 1 to 16 years of age with erosive esophagitis has not been established. If a patient does not respond to eight weeks of treatment, an additional four weeks of treatment may be given.
k As triple therapy with amoxicillin 1,000 mg twice daily plus clarithromycin 500 mg twice daily. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.
l As combination therapy with clarithromycin 500 mg three times daily. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.
m Controlled studies did not extend beyond 12 months. For omeprazole magnesium only, a dosage reduction to 10 mg once daily is recommended for patients with hepatic impairment (Child-Pugh Class A, B or C) and Asian patients when used for the maintenance of healing of erosive esophagitis. patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole for more than five years.
n The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. Daily doses higher than 240 mg or administered more than six days have not been studied.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Dexlansoprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in patients < 12 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required for mild (Child-Pugh Class A) hepatic impairment. A maximum dose of 30 mg should be considered in patients with moderate (Child-Pugh Class B) hepatic impairment. Capsules and SoluTabs are not recommended in patients with severe (Child-Pugh Class C) hepatic impairment.	There are no studies with use in pregnant women to inform a drug-associated risk. Unknown whether excreted in human milk; use with caution.
Esomeprazole magnesium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in patients ≥ 1 month of age.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate (Child-Pugh Class A or B) liver impairment. Hepatic dose adjustment is required in patients with severe (Child-Pugh Class C) liver	There are no adequate and well-controlled studies in pregnant women; use with caution. Likely present in human milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
				impairment; do not exceed a dose of 20 mg.	
Esomeprazole sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in patients ≥ 1 month of age.	No dosage adjustment required.	Dose adjustments are needed in patients with liver impairment: For patients with bleeding gastric or duodenal ulcers and mild to moderate liver impairment (Child-Pugh Class A and B): Maximum continuous infusion of 6 mg/hr For patients with severe liver impairment (Child Pugh Class C): Maximum continuous infusion of 4 mg/hr	There are no adequate and well-controlled studies in pregnant women; use with caution. Likely present in human milk; use with caution.
Esomeprazole strontium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in pediatrics have not been established.	No dosage adjustment required in patients with mild to moderate renal impairment. Due to lack of data, not recommended in patients with severe renal impairment.	No dosage adjustment required for patients with mild-to- moderate (Child-Pugh Class A or B) liver impairment. Hepatic dose adjustment is required in patients with severe (Child-Pugh Class C) liver impairment; do not exceed a dose of 24.65 mg.	Pregnancy Category C Limited published data indicate that esomeprazole and strontium are present in human milk; a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Lansoprazole	No dosage adjustment required.	Approved for use in patients > 1 year of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered in severe hepatic impairment. In patients with various degrees of	Pregnancy Category B Unknown whether excreted in human milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
				chronic hepatic impairment, an increase in the mean area under the curve of up to 500% was observed at steady state compared to healthy subjects.	
Omeprazole magnesium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in patients > 1 month of age.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis; dose reduction in Asian patients recommended for the same indication.	There are no adequate and well-controlled studies in pregnant women; use with caution. Likely present in human milk; use with caution.
Omeprazole/ sodium bicarbonate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in patients < 18 years of age have not been established.	No dosage adjustment required.	Hepatic dose adjustment should be considered for the maintenance of healing of erosive esophagitis; dose reduction in Asian patients recommended for the same indication.	Pregnancy Category C Excreted in breast milk (< 7%) after a 20 mg dose; discontinue nursing or discontinue drug.
Pantoprazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved in children ≥ 5 years of age.	No dosage adjustment required.	No dosage adjustment required.†	Pregnancy Category B Detection in human milk after a 40 mg dose; discontinue nursing or discontinue drug
Rabeprazole	No dosage adjustment required.	Approved for use in children ≥ 12 years of age (ACIPHEX) and children 1 to 11 years of age (ACIPHEX SPRINKLE).	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate liver impairment. Caution is advised for patients with severe liver impairment.	No available human data on use in pregnant women to inform the drug-associated risk. Unknown whether excreted in human milk; use with caution.

†Doses > 40 mg/day have not been studied in patients with hepatic impairment.
* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- PPIs are the most potent inhibitors of gastric acid secretion available.
- All of the PPIs are FDA-approved for the treatment and maintenance of GERD and, with the exception of dexlansoprazole and omeprazole with sodium bicarbonate, for the treatment of pathological hypersecretory conditions.
- With the exception of dexlansoprazole, esomeprazole sodium, omeprazole with sodium bicarbonate, and pantoprazole, all of the PPIs are approved for the eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence.
- Dexlansoprazole and omeprazole with sodium bicarbonate are the only PPIs that are not FDA-approved for use in children. Dexlansoprazole is indicated in patients ≥ 12 years of age, while omeprazole with sodium bicarbonate is only indicated in adults.
- All PPIs are available in delayed-release oral formulations, with the exception of esomeprazole sodium, pantoprazole IV, and omeprazole with sodium bicarbonate. All oral products can be dosed once daily.
- Dexlansoprazole is uniquely formulated to release at different time intervals, at two different sites of the small intestine. The clinical significance of this is unknown.
- Esomeprazole magnesium, omeprazole magnesium, and pantoprazole are available as granules for a delayed-release oral suspension. Omeprazole with sodium bicarbonate is available as a powder for oral suspension. Rabeprazole is available in a sprinkle delayed-release capsule formulation.
- Esomeprazole strontium was approved in August 2013 without a proprietary name. Available generically and approved based on studies of esomeprazole magnesium, esomeprazole strontium has the same indications as esomeprazole magnesium with the exception of use in pediatric patients. It is a different salt formulation available in two unique strengths: 24.65 and 49.3 mg, equivalent to esomeprazole magnesium 20 and 40 mg, respectively.
- Esomeprazole magnesium, lansoprazole, omeprazole, omeprazole magnesium, and omeprazole with sodium bicarbonate are also available in OTC formulations.
- Esomeprazole sodium and pantoprazole are available in intravenous formulations for short-term use in patients unable to take medications by mouth.
- Rabeprazole, esomeprazole magnesium, esomeprazole strontium, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are all available generically, however some formulations (e.g., orally disintegrating tablets [solutabs] and oral suspensions) remain available only as brands.
- Current medical evidence demonstrates that PPI therapy is highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as erosive esophagitis and symptomatic GERD.
    - Meta-analyses and direct comparator trials demonstrate that lansoprazole, omeprazole, pantoprazole, and rabeprazole have comparable healing rates, maintenance of healing, and symptomatic relief of GERD (Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001).
    - A few trials report statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known (Richter, Kahrilas, Sontag et al, 2001).
    - There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole (Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Richter et al, 2001).
    - Subgroup analyses in two trials noted better healing rates with esomeprazole in patients with more severe disease (Labenz et al, 2005[a]; Schmitt et al, 2006).
    - Evidence suggests that there is no major difference in efficacy among the various PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.
    - Currently, there is a lack of head-to-head studies of dexlansoprazole with the other agents in this class.
- Clinical studies have demonstrated that PPIs are also highly effective in the treatment of peptic ulcer disease caused by chronic NSAID therapy or *H. pylori* infection when coupled with antibiotics.
    - Meta-analyses and head-to-head trials comparing PPIs to each other have shown comparable rates of eradication when administered at comparable doses and paired with comparable antibiotic regimens.
    - Results of meta-analyses suggest that regimens containing the new generation PPIs (esomeprazole and rabeprazole) may be more effective than the other PPIs at eradicating *H. pylori* (McNicholl et al, 2012; Xin et al, 2016).

- Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.

- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. No treatment guidelines recommend one PPI over another or one formulation of a PPI over another.

REFERENCES

- Abraham NS, Hlatky MA, Antman EM, et al; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010;56(24):2051-2066.
- ACIPHEX prescribing information. Eisai Inc. Woodcliff Lake, NJ. October 2016.
- ACIPHEX SPRINKLE prescribing information. Eisai Inc. Woodcliff Lake, NJ. October 2016.
- American Gastroenterological Association Institute Medical Position Panel. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135(4):1383-1391.
- American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.
- Armstrong D, Talley NJ, Lauritsen K, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Aliment Pharmacol Ther. 2004;20(4):413-21.
- Bardhan KD, Van Rensburg C. Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux esophagitis. Aliment Pharmacol Ther. 2001;15:1585-91.
- Bazzoli F, Pozzato P, Zagari M, et al. Efficacy of lansoprazole in eradicating Helicobacter pylori: a meta-analysis. Helicobacter. 1998;3(3):195-201.
- Bergsland E. Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma). UpToDate Web site. http://www.uptodate.com/contents/management-and-prognosis-of-the-zollinger-ellison-syndrome-gastrinoma?source=search_result&search=zollinger&selectedTitle=2%7E81. Updated February 25, 2016. Accessed March 13, 2017.
- Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared to omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther. 2001;23(7):998-1017.
- Castell D, Bagin R, Goldlust B, et al. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;21(12):1467-74.
- Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared to lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-83.
- Chan FKL, Lanas A, Scheiman J, et al. Celecoxib vs omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomized trial. Lancet. 2010;376:173-9.
- Chey W, Huang B. Jackson RL. Lansoprazole and esomeprazole in symptomatic GERD: a double-blind, randomized, multicentre trial in 3000 patients confirms comparable symptom relief. Oesophagitis. Clin Drug Invest. 2003;23(2):69-84.
- Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017; 112:212-38.
- Choi HS, Park DI, Hwang SJ, et al. Double-dose, new-generation proton-pump inhibitors do not improve eradication rate. Helicobacter. 2007; 2(6):638-42.
- Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension vs intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med. 2005;33(4):760-5.
- Dean L. PubMed Clinical Q&A [Internet]. Bethesda, MD. National Center for Biotechnology Information. Comparing Proton Pump Inhibitors. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004954/. Accessed March 14, 2017.
- Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastroesophageal reflux disease. Scand J Gastroenterol. 2000;35:1245-50.
- Devault KR, Johanson JF, Johnson DA, et al. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006 Jul;4(7):852-9.
- DEXILANT prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. October 2016.
- DEXILANT SOLUTAB prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. October 2016.
- Drugs@FDA. U.S. Food and Drug Administration. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 14, 2017.
- Edwards SJ, Lind T, Lundell L. Systematic review of proton-pump inhibitors for the acute treatment of reflux oesophagitis. Aliment Pharmacol Ther. 2001;15(11):1729-36.
- Esomeprazole strontium prescribing information. R2 Pharma, LLC. Petal, MS. September 2016.
- Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effect of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2009;29:1261-72.
- Fass R, Johnson DA, Orr WC, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol. 2011 Mar;106(3):421-31.
- Fass R, Inadomi J, Han C, et al. Maintenance of heartburn relief after step-down from twice-daily proton pump inhibitor to once-daily dexlansoprazole modified release. Clin Gastroenterol Hepatol. 2012 Mar;10(3):247-53.
- Felga G, Silva FM, Barbuti RC, et al. Clarithromycin-based triple therapy for Helicobacter pylori treatment in peptic ulcer patients. J Infect Dev Ctries. 2010 Nov 24;4(11):712-6.
- Fennerty MB, Johanson JF, Hwang C, et al. Efficacy of esomeprazole 40 mg vs lansoprazole 30 mg for healing moderate-to-severe erosive oesophagitis. Aliment Pharmacol Ther. 2005;21(4):455-63.

- Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology. 2017 Mar;152(4):706-15.
- Fujimoto K, Hongo M; Maintenance Study Group. Safety and efficacy of long-term maintenance therapy with oral dose of rabeprazole 10 mg once daily in Japanese patients with reflux esophagitis. Intern Med. 2011;50(3):179-88.
- Gisbert JP, Khorrami S, Calvet X, et al. Pantoprazole-based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2004;16(1):89-99.
- Gisbert JP, Khorrami S, Calvet X, et al. Systematic review: rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;17(6):751-64.
- Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004;36(4)253-9.
- Goh KL, Benamouzig R, Sander P, et al; EMANCIPATE. Efficacy of pantoprazole 20 mg daily compared to esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial-the EMANCIPATE study. Eur J Gastroenterol Hepatol. 2007;19(3):205-11.
- Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol. 2016 Apr;73(4):410-6.
- Haddad I, Kierkus J, Tron E, et al. Efficacy and Safety of Rabeprazole in Children (1-11 Years) with Gastroesophageal Reflux Disease: A Multicenter, Double-Blind, Parallel-Group Study. J Pediatr Gastroenterol Nutr. 2013. 57(6):798-807. doi: 10.1097/MPG.0b013e3182a4e718
- Howden CW, Ballard EDI, Robieson W. Evidence for therapeutic equivalence of lansoprazole 30 mg and esomeprazole 40 mg in the treatment of erosive oesophagitis. Clin Drug Invest. 2002;22(2):99-109.
- Howden CW, Larsen LM, Perez MC, et al. Clinical trial: efficacy and safety of dexlansoprazole MR 60 mg and 90 mg in healed erosive oesophagitis – maintenance of healing and symptom relief. Aliment Pharmacol Ther. 2009;30:895-907.
- Hsu PI, Lai KH, Lin CK, et al. A prospective randomized trial of esomeprazole-vs pantoprazole-based triple therapy for Helicobacter pylori eradication. Am J Gastroenterol. 2005;100(11):2387-92.
- Jackson LR, Peterson ED, McCoy LA , et al. Impact of proton pump inhibitor use on the comparative effectiveness and safety of prasugrel versus clopidogrel: insights from the treatment with adenosine diphosphate receptor inhibitors: longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study. J Am Heart Assoc. 2016 Oct;5:e003824.
- Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared to omeprazole in reflux oesophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther. 2000;14:1249-58.
- Kahrilas PJ, Shaheen NJ, Vaezi MF, et al; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008 Oct;135(4):1383-91,1391.e1-5.
- Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013 Mar;108(3):308-28.
- Katz PO, Koch FK, Ballard ED, et al. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with nighttime GERD symptoms. Aliment Pharmacol Ther. 2007 Jan 15;25(2):197-205.
- Kinoshita Y, Ashida K, Hongo M; Japan. Rabeprazole Study Group for NERD. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. Aliment Pharmacol Ther. 2011 Jan;33(2):213-24.
- Klok RM, Postma MJ, van Hout BA, et al. Meta-analysis: comparing the efficacy of proton-pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003;17(10):1237-45.
- Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):230-43. doi: 10.1097/MPG.0b013e3182227e90.
- Labenz J, Armstrong D, Lauritsen K, et al. A randomized comparative study of esomeprazole 40 mg vs pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005[a];21(6):739-46.
- Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Aliment Pharmacol Ther. 2005[b];22(9):803-11.
- Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012 Mar;107(3):345-60.
- Laine L, Katz PO, Johnson DA, et al. Randomised clinical trial: a novel rabeprazole extended release 50 mg formulation vs. esomeprazole 40 mg in healing of moderate-to-severe erosive oesophagitis - the results of two double-blind studies. Aliment Pharmacol Ther. 2011 Jan;33(2):203-12.
- Lanza FL, Chan FKL, Quigley EMM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38.
- Lauritsen K, Devière J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003;17(3):333-41.
- Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016 Feb;176(2):238-46.
- Lightdale CJ, Schmitt C, Hwang C, et al. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci. 2006 May;51(5):852-7.
- Malfertheiner P, Megraud F, O'Morain CA, et al.; European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. Gut. 2012 May;61(5):646-64.
- McNicholl AG, Linares PM, Nyssen OP, et al. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of Helicobacter pylori infection. Aliment Pharmacol Ther. 2012 Sep;36(5):414-25.
- Melloni C, Washam JB, Jones WS, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy. Circ Cardiovasc Qual Outcomes. 2015;8:47-55.
- Metz DC, Howden CW, Perez MC, et al. Clinical trial dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive esophagitis. Aliment Pharmacol Ther. 2009;29:742-54.
- Mönnikes H, Schwan T, van Rensburg C, et al. Randomised clinical trial: sustained response to PPI treatment of symptoms resembling functional dyspepsia and irritable bowel syndrome in patients suffering from an overlap with erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2012 Jun;35(11):1279-89.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Zollinger-Ellison syndrome. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/zollinger-ellison-syndrome. Accessed March 13, 2017.
- NEXIUM prescribing information. AstraZeneca LP. Wilmington, DE. December 2016.
- NEXIUM IV prescribing information. AstraZeneca LP. Wilmington, DE. December 2016.
- NEXIUM 24HR capsules prescribing information. Pfizer Consumer Healthcare. Madison, NJ. May 2016.

- NEXIUM 24HR tablets prescribing information. Pfizer Consumer Healthcare. Madison, NJ. February 2016.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 14, 2017.
- Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomized, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Dig Liver Dis. 2005;37:741-50.
- Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton-pump inhibitors for the short-term treatment of esophagitis in elderly patients. World J Gastroenterol. 2007;13(33):4467-72.
- Pouchain D, Bigard MA, Liard F, et al. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial. BMC Gastroenterol. 2012 Feb 23;12:18.
- PREVACID prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. October 2016.
- PREVACID 24HR prescribing information. GlaxoSmithKline Consumer Healthcare Holdings, LLC. Warren, NJ. April 2016.
- PRILOSEC prescribing information. AstraZeneca LP. Wilmington, DE. December 2016.
- PRILOSEC OTC product information. Procter and Gamble. Cincinnati, OH. December 2016.
- PROTONIX prescribing information. Wyeth Pharmaceuticals Inc. Philadelphia, PA. February 2017.
- PROTONIX IV prescribing information. Wyeth Pharmaceuticals Inc. Philadelphia, PA. November 2016.
- Ramdani A, Mignon M, Samoyeau R. Effect of pantoprazole vs other proton-pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. Gastroenterol Clin Biol. 2002;26(4):355-9.
- Regula J, Butruk E, Dekkers CP, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole vs omeprazole. Am J Gastroenterol. 2006 Aug;101(8):1747-55.
- Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared to omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656-65.
- Richter JE, Kahrilas PJ, Sontag SJ, et al. Comparing lansoprazole and omeprazole in onset of heartburn relief: results of a randomized, controlled trial in erosive esophagitis patients. Am J Gastroenterol. 2001;96:3089-98.
- Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart. 2011 May;97(10):797-802.
- Schmitt C, Lightdale CJ, Hwang C, et al. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006 May;51(5):844-50.
- Scholten T, Gatz G, Hole U. Once-daily pantoprazole 40 mg and esomeprazole 40 mg have equivalent overall efficacy in relieving GERD-related symptoms. Aliment Pharmacol Ther. 2003;18(6):587-94.
- Shah NH, Lependu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS ONE. 10(6):e0124653.
- Shaheen NJ, Falk GW, Iyer PG, Gerson L. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30-50.
- Sharma VK, Leontiadis GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. Aliment Pharmacol Ther. 2001;15(2):227-31.
- Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation – results from two randomized controlled studies. Aliment Pharmacol Ther. 2009;29:731-41.
- Sherwood MW, Melloni C, Jones WS, et al. Individual proton pump inhibitors and outcomes in patients with coronary artery disease on dual antiplatelet therapy: a systematic review. J Am Heart Assoc. 2015;4(11):1-8.
- Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol. 2011 Jun;46(6):724-35.
- Talley NJ; American Gastroenterological Association. American Gastroenterological Association Medical Position Statement: Evaluation of dyspepsia. Gastroenterology. 2005[a];129(5):1753-5.
- Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005[b];100(10):2324-37.
- Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ. 2008 Aug;179(4):319-26.
- Tsai HH, Chapman R, Shepherd A, et al. Esomeprazole 20 mg on-demand is more acceptable to patients than continuous lansoprazole 15 mg in the long-term maintenance of endoscopy-negative gastro-oesophageal reflux patients: the COMMAND Study. Aliment Pharmacol Ther. 2004;20:657-65.
- Ulmer HJ, Beckerling A, Gatz G. Recent use of proton-pump inhibitor-based triple therapies for the eradication of H pylori: a broad data review. Helicobacter. 2003;8(2):95-104.
- van Pinxteren B, Sigterman KE, Bonis P, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD002095.
- Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498-547.
- Vergara M, Vallve M, Gisbert JP, et al. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003;18:647-54.
- Wang X, Fang JY, Lu R, et al. A meta-analysis: comparison of esomeprazole and other proton-pump inhibitors in eradicating Helicobacter pylori. Digestion. 2006;73(2-3):178-86.
- Welage LS. Pharmacologic features of proton-pump inhibitors and their potential relevance to clinical practice. Gastroenterol Clin North Am. 2003;32(3 Suppl):S25-35.
- Wolfe MM. Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders. UpToDate Web site. http://www.uptodate.com/contents/overview-and-comparison-of-the-proton-pump-inhibitors-for-the-treatment-of-acid-related-disorders?source=search_result&search=proton+pump+inhibitors&selectedTitle=1%7E150. Updated June 2, 2016. Accessed March 14, 2017.
- Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118(2 Suppl 1):S9-31.

- Wu IC, Wu DC, Hsu PI, et al. Rabeprazole- vs esomeprazole-based eradication regimens for H pylori infection. Helicobacter. 2007;12(6):633-7.
- Xie Y, Bowe B, Li, T, et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Feb.
- Xin Y, Manson J, Govan L. Pharmacological regimens for eradication of Helicobacter pylori: an overview of systematic reviews and network meta-analysis. BMC Gastroenterol. 2016 Jul; 16(1):80.
- Yepuri G, Sukhovershin R, Nazari-Shafti TZ, et al. Proton pump inhibitors accelerate endothelial senescence. Circ Res. 2016 Jun;118(12):e36-42.
- ZEGERID prescribing information. Santarus, Inc. San Diego, CA. October 2016.
- ZEGERID OTC prescribing information. Bayer Healthcare LLC. Whippany, NJ. March 2016.

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Therapeutic Class Overview
Inflammatory Bowel Disease Agents

INTRODUCTION

- Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding, fatigue, and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic, and lifestyle factors (UpToDate, 2017[b]).
- Complications of IBD include hemorrhoids, rectal fissures, fistulas, peri-rectal and intra-abdominal abscesses, and colon cancer. Possible extra-intestinal complications include hepatobiliary complications, anemia, arthritis and arthralgias, uveitis, skin lesions, and mood and anxiety disorders (Bernstein et al, 2015).
- Ulcerative colitis (UC) and Crohn's disease (CD) are two forms of IBD that differ in pathophysiology and presentation; as a result of these differences, the approach to the treatment of each condition often differs (UpToDate, 2017[a]).
- UC is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus (Kornbluth et al 2010, UpToDate 2017[b]).
- CD can involve any part of the gastrointestinal tract and is characterized by transmural inflammation and "skip lesions". Transmural inflammation may lead to fibrosis, strictures, microperforations, and fistulae (UpToDate 2017[b]).
- The immune system is known to play a critical role in the underlying pathogenesis of IBD. It is suggested that abnormal responses of both innate and adaptive immunity mechanisms induce aberrant intestinal tract inflammation in IBD patients (Geremia et al, 2014).
- Precise incidence and prevalence of CD and UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggests that the United States (U.S.) incidence rate of UC varies between 2.2 to 14.3 per 100,000 persons and incidence of CD varies from 3.1 to 14.6 per 100,000 persons. Prevalence rate of IBD has been estimated to be as high as 439 per 100,000 persons with as many as 1 to 1.3 million persons in the U.S. suffering from these diseases (Centers for Disease Control [CDC], 2015).
- Some risk factors for IBD include age, gender, race, ethnicity, genetics, smoking status, and dietary considerations.
    - The typical age of onset of IBD is between 15 and 40 years, while a second peak between ages 50 and 80 years has been noted.
    - Caucasians tend to have a higher incidence of IBD compared to Hispanic and Black populations. Additionally, ethnic and racial differences may be related to environmental and lifestyle factors as well as underlying genetic differences.
    - Genetic susceptibility to IBD is not completely understood; however, it is estimated that nearly 10 to 25% of individuals afflicted with IBD have a first-degree relative with IBD.
    - Smoking status affects CD and UC differently, being associated with an increased risk with CD and a decreased risk with UC.
    - Dietary factors have been associated as risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, processed, fried, and sugar-laden foods are associated with an increased risk of developing CD and possibly UC (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2014).
- The goals for the treatment of IBD include resolution of intestinal inflammation and healing of the mucosa; elimination of symptoms while minimizing side effects; maintenance of corticosteroid-free remission; prevention of complications, hospitalization, and surgery; and maintenance of good nutritional status (Bernstein et al, 2015).
- Current pharmacotherapy for UC consists of four major drug classes: 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, infliximab, infliximab-dyyb, adalimumab, golimumab, vedolizumab) (Micromedex, 2017).
    - Choice of therapy is based on several factors, including disease severity, anatomic extent, and response to prior therapies *(*Kornbluth et al, 2010*).*
    - Inflammation that is distal is limited to below the descending colon and within reach of topical therapy. Inflammation that extends proximal to the descending colon requires systemic medication *(*Kornbluth et al 2010*)*.
- Although the specific Food and Drug Administration (FDA)-approved indications of the oral 5-ASA derivative preparations vary, these agents are used in the treatment and maintenance of remission of UC. The oral 5-ASA

derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine. The newer 5-ASA derivatives, including balsalazide, mesalamine, and olsalazine, were developed to avoid the side effects associated with sulfasalazine while maintaining its overall therapeutic benefits.

- Budesonide (UCERIS®) is available in an extended release tablet which delays the release of budesonide until it reaches the site of action. Budesonide is also available as a rectal foam (UCERIS). Budesonide capsules (ENTOCORT® EC) are approved for use for the treatment and maintenance of remission of CD; however, they will not be included in this review.
- Sulfasalazine (AZULFIDINE® EN-tabs) is also FDA-approved for the treatment of rheumatoid arthritis nonresponsive to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDS) and for pediatric polyarticular-course juvenile rheumatoid arthritis.
- Other injectable biologic response modifiers known as monoclonal antibodies (MABs) are also approved to treat UC and/or CD including the tumor necrosis factor (TNF) inhibitors (e.g., CIMZIA [certolizumab pegol], HUMIRA [adalimumab], SIMPONI [golimumab], INFLECTRA [infliximab-dyyb], and REMICADE [infliximab]). In 2014, the alpha-4 beta-7 (α4β7) integrin receptor antagonist, ENTYVIO (vedolizumab) was approved for treatment of moderately to severely active UC and CD in adult patients who have had an inadequate response with, lost response to, or were intolerant to a TNF inhibitor or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Additional injectable, humanized MABs are being studied for the treatment of various forms of IBD. These are reviewed in the Immunomodulators Class.
- The scope of this review will focus upon the oral and topical agents outlined in Table 1 for their respective FDA-approved, gastrointestinal-related indications.
- Medispan Therapeutic Class: Inflammatory Bowel Agents

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
APRISO® (mesalamine) ER capsule	Salix Pharmaceuticals	10/31/2008	-
ASACOL® HD (mesalamine) DR tablet	various	05/29/2008	✔
AZULFIDINE® (sulfasalazine) tablet	various	06/20/1950	✔
AZULFIDINE EN-tabs (sulfasalazine) DR tablet	various	04/06/1983	✔
CANASA® (mesalamine) rectal suppository	Forest Labs	11/05/2004	-
COLAZAL® (balsalazide) capsule	various	07/18/2000	✔
DELZICOL™ (mesalamine) DR capsule	Warner Chilcott	02/01/2013	-
DIPENTUM® (olsalazine) capsule	Meda Pharmaceuticals	07/31/1990	-
GIAZO® (balsalazide) tablet	Salix Pharmaceuticals	02/03/2012	-
LIALDA® (mesalamine) DR tablet	Shire US, Inc.	01/16/2007	-
PENTASA® (mesalamine) CR capsule	Shire US, Inc.	05/10/1993	-
ROWASA® (mesalamine) rectal enema suspension	various	12/24/1987	✔
sfROWASA® (mesalamine) rectal enema suspension (sulfite-free)	Meda Pharms	06/20/2008	-
UCERIS (budesonide) ER tablet	Salix Pharmaceuticals	01/14/2013	-
UCERIS (budesonide) rectal foam	Salix Pharmaceuticals	10/07/2014	-

CR=controlled release, DR=delayed release, ER=extended release
ASACOL (mesalamine) by Warner Chilcott was discontinued by the manufacturer in the spring of 2013 due to a business decision. A generic is not currently available.

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mildly to moderately active UC in patients ≥ 5 years of age	✔ (COLAZAL)†	-	✔ (DELZICOL)	-	-

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mildly to moderately active UC in males ages 18 years and older	✔ (GIAZO)‡	-	-	-	-
Treatment of moderately active UC in adults	-	-	✔ (ASACOL HD)*	-	-
Induction of remission in adults with active, mild to moderate UC	-	✔ (UCERIS tablet)	✔ (LIALDA)	-	-
Induction of remission in adults with active mild to moderate distal UC extending up to 40 cm from the anal verge	-	✔ (UCERIS rectal foam)	-	-	-
Maintenance of remission of UC in adults	-	-	✔ (APRISO; DELZICOL; LIALDA)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	-	✔	-
Induction of remission and for the treatment of patients with mildly to moderately active UC	-	-	✔ (PENTASA)	-	-
Treatment of mildly to moderately active ulcerative proctitis	-	-	✔ (CANASA)	-	-
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	-	✔ (ROWASA; sfROWASA)	-	-
Treatment of mild to moderate UC, and as adjunctive therapy in severe UC	-	-	-	-	✔ (AZULFIDINE; AZULFIDINE EN-tabs**)
Prolongation of the remission period between acute attacks of UC	-	-	-	-	✔ (AZULFIDINE) AZULFIDINE EN-tabs**)
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]	-	-	-	-	✔ (AZULFIDINE EN-tabs)
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs	-	-	-	-	✔ (AZULFIDINE EN-tabs)

*Safety and effectiveness of ASACOL HD beyond 6 weeks have not been established.
**AZULFIDINE EN-TABS are specifically indicated in patients with UC who cannot tolerate sulfasalazine tablets due to gastrointestinal intolerance when the gastrointestinal intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites.
†Safety and effectiveness of balsalazide beyond eight weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

‡Effectiveness in female patients was not demonstrated in clinical trials. Safety and effectiveness of GIAZO beyond eight weeks have not been established.

(Prescribing information: APRISO, 2016; ASACOL HD, 2016; AZULFIDINE, 2014; AZULFIDINE EN-TABS, 2016; CANASA, 2016; COLAZAL, 2016; DELZICOL, 2016; DIPENTUM, 2014; GIAZO, 2016; LIALDA, 2015; PENTASA, 2015; ROWASA, 2013; sfROWASA, 2013; UCERIS tablet, 2016; UCERIS rectal foam, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Oral therapy

- Multiple systematic reviews have been published evaluating randomized clinical trials of mesalamine products for UC. No significant differences in safety or efficacy between the mesalamine products have been found in the systematic reviews.
  - In a 2013 Cochrane review of 17 randomized clinical trials (N = 2,925), the efficacy and safety of oral mesalamine products used for induction and maintenance of remission of UC were evaluated. The primary outcomes were failure to induce global or clinical remission or improvement, and failure to maintain global or clinical remission (relapse). Products included balsalazide, olsalazine, PENTASA, ASACOL, LIALDA, and three mesalamine products which are not available in the U.S. For the failure to induce global or clinical remission in mild to moderately active UC endpoint, there was no significant difference between the 5-ASA formulations (balsalazide, PENTASA, olsalazine, LIALDA, mesalamine, and 5-ASA micropellets) and the comparator group (ASACOL and two mesalamine formulations) (11 studies, N = 1968, 50% vs. 52%, pooled relative risk [RR] 0.94, 95% confidence interval [CI], 0.86 to 1.02, I^2 = 0%, P = 0.11). For failure to induce global or clinical remission or improvement, a total of eight studies with 1,647 patients were evaluated, and results demonstrated that there was no difference between the 5-ASA products (balsalazide, PENTASA, olsalazine, LIALDA, and 5-ASA micropellets) and the 5-ASA comparators (ASACOL, two mesalamine formulations, and PENTASA) (30% vs. 35%, pooled RR 0.89, 95% CI, 0.77 to 1.01, I^2 = 0%, P = 0.08) using a fixed-effect model. Note that PENTASA was on both sides of the comparison for this endpoint. For the failure to maintain global or clinical or endoscopic remission at 12 months, there was no difference between the 5-ASA formulations (balsalazide, PENTASA, and olsalazine) and the comparators (ASACOL, mesalamine) in five studies (N = 457) (38% vs. 37%, pooled RR 1.01, 95% CI, 0.80 to 1.28, I^2 = 39%, P = 0.95). The incidences of adverse events between the various formulations were not significantly different. Risk of bias was low for most study factors; however, one study was single-blind, and three were open-label. There were numerous products in this systematic review which are not currently available in the U.S. (Feagan et al, 2013).
  - Another systematic review evaluated once daily oral mesalamine compared to conventional dosing regimens of oral mesalamine for induction and maintenance of remission of UC in 11 studies with 4,070 patients. Of the 11 studies, five studies were single-blind, and one study was performed in an open-label manner. Products assessed were LIALDA, ASACOL, PENTASA, and SALOFALK (mesalazine - not available in the U.S.). Failure to induce global or clinical remission was not different between once daily and conventional dosing of mesalamine (three studies, N = 738; pooled RR 0.95, 95% CI, 0.82 to 1.10; I^2 = 0%). No difference was observed between dosing regimens for the failure to maintain global or clinical remission at 12 months (five studies, N = 1,394; pooled RR 0.92, 95% CI, 0.83 to 1.03, I^2 = 40.9%). Rates of medication adherence or adverse events between once daily and conventional dosing regimens of mesalamine were not significantly different. The authors noted that adherence rates in clinical trials may be higher than real world usage (Feagan and MacDonald, 2012).
  - A 2016 Cochrane review of 53 studies with 8,548 patients with UC evaluated the oral 5-ASA preparations and sulfasalazine for the induction of active UC remission. The newer 5-ASA derivatives were “superior” to placebo with 71% of 5-ASA patients failing to enter clinical remission compared to 83% for placebo (11 studies; N = 2,387; RR 0.86, 95% CI, 0.82 to 0.89). No statistically significant differences in efficacy between 5-ASA and sulfasalazine were observed with 54% of 5-ASA-treated patients and 58% of sulfasalazine-treated patients who failed to enter remission (eight studies; N = 526; RR 0.90, 95% CI, 0.77 to 1.04). Adherence did not appear to be enhanced by once daily dosing in the clinical trials; however, it is not known if once daily dosing would improve adherence in the community setting. Failure to enter clinical remission rates were 45% for once daily vs. 48% for conventional dosing regimens (four studies; N = 944; RR 0.94, 95% CI, 0.83 to 1.07). No significant differences among the 5-ASA products for safety and efficacy were found (Wang et al, 2016[a]).
  - In a 2016 Cochrane review of 41 studies with 8,928 patients, all 5-ASA formulations were “superior” to placebo for maintenance of clinical or endoscopic remission of UC. Relapse rates were 41% for 5-ASA-treated patients and 58% for placebo-treated patients (seven studies; N = 1,298; RR 0.69; 95% CI, 0.62 to 0.77). Sulfasalazine was

found to have a statistically significant benefit over 5-ASA in the maintenance of UC when looking at all trials at study endpoint (12 studies; N = 1,655; RR 1.14, 95% CI, 1.03 to 1.27); however, when trials of 12 months or longer were only evaluated, there was no longer a difference between sulfasalazine and 5-ASA (eight studies; N = not reported; RR 1.10, 95% CI, 0.98 to1.23). No significant difference for efficacy was demonstrated between once daily and conventional dosing regimens with 29% of once daily-treated patients relapsed over 12 months vs. 31% of conventionally dosed patients (eight studies; N = 3,127; RR 0.91, 95% CI, 0.82 to 1.01). For adherence, failure to adhere to the regimen was reported in 11% of once-daily-treated patients compared to 9% of patients in the conventional dosing group (six studies; N = 1,462; RR 1.22, 95% CI, 0.91 to 1.64). No significant difference in efficacy was found when comparing the various 5-ASA formulations. Relapse rate was 44% in the 5-ASA group vs. 41% in the 5-ASA comparator group (six studies; N = 707; RR 1.08, 95% CI, 0.91 to 1.28). No statistically significant differences were found for the incidence of adverse events between 5-ASA and placebo, 5-ASA and sulfasalazine, once daily and conventionally dosed 5-ASA, 5-ASA and comparator 5-ASA formulations, and 5-ASA dose ranging studies (Wang et al, 2016[b]).
    - A meta-analysis of 10 studies that evaluated mesalamine once daily vs. multiple daily dosing regimens in 3,410 patients with quiescent UC was conducted to determine the efficacy in preventing a relapse. The intention to treat analysis found that mesalamine once daily (26.3%) was as effective as multiple daily doses (26.5%) (eight studies, RR 1.00, 95% CI, 0.89 to 1.12, I^2 = 41%, P = 0.105). An analysis of the efficacy of once daily vs. multiple daily dosing of mesalamine for inducing remission in active UC found that remission was not observed in 29.8% of patients on once daily mesalamine and 37.8% of patients receiving multiple daily doses. The risk of failure to achieve remission was higher with multiple daily doses (two studies, RR 0.80; 95% CI, 0.64 to 0.99, I^2 = 21.6%, P = 0.259). When evaluating the same outcome on a per-protocol analysis, there was no significant difference between the two groups. No significant differences in adverse events were observed between the two groups (Tong et al, 2012).
    - In another 2012 meta-analysis, 9 of 10 studies included in the Tong et al analysis were evaluated by another group (Zhu et al, 2012). There were no significant differences for once daily compared to more frequent dosing (twice or three times daily) of mesalamine for UC for the maintenance of clinical remission, endoscopic remission, maintenance of combined clinical and endoscopic remission, and the overall incidence of adverse events.
- A Cochrane review evaluated oral budesonide for induction of remission in UC. A total of six studies (N = 1,808) were evaluated. Budesonide MMX 9 mg was superior to placebo for inducing remission at eight weeks (15% vs. 7%, respectively; 3 studies, N = 900; RR 2.25, 95% CI, 1.50 to 3.39; moderate quality of evidence). An analysis of two studies with budesonide MMX 6 mg showed that it was not superior to placebo for induction of remission (11% vs. 6%, respectively; two studies, N = 440; RR 1.80, 95% CI, 0.94 to 3.42; low quality of evidence). Budesonide (ENTOCORT EC) was significantly less likely to induce clinical remission than oral mesalamine after eight weeks (one study, N = 343; RR 0.72, 95% CI 0.57 to 0.91; moderate quality of evidence). However, another study discovered no difference in remission rates between budesonide MMX 9 mg and mesalamine (one study; N = 247; RR 1.48, 95% CI 0.81 to 2.71; low quality of evidence). In a comparison of the two budesonide formulations, there was no difference in remission rates between budesonide MMX 9mg and budesonide 9 mg (one study, N = 212; RR 1.38, 95%CI, 0.72 to 2.65; low quality of evidence). More studies are needed to compare budesonide to other UC therapies (Sherlock et al, 2015).
- ASACOL (mesalamine) is not currently available; however, efficacy data of DELZICOL was based on clinical trial data with ASACOL (DELZICOL prescribing information, 2015).

<u>Topical therapy</u>

- According to a meta-analysis comparing rectal 5-ASA therapy to either placebo or other active agents for the treatment of distal disease, rectal 5-ASA was superior to placebo and rectal corticosteroids. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement (Marshall et al, 2010). A 2012 smaller meta-analysis found that rectal 5-ASA therapy was superior to placebo and similar to oral 5-ASA on rates of symptomatic remission and endoscopic remission. No dose response relationship for 5-ASA enemas or other rectal dosage forms has been observed (Marshall et al, 2012).
- A meta-analysis found greater efficacy with topical mesalamine than placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat of three. Time to relapse was longer with topical mesalamine in the two trials, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy (Ford et al, 2012[b]).
- Budesonide rectal foam was compared to placebo in two randomized, Phase 3 trials in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. Compared to placebo, a significantly greater proportion of patients receiving budesonide rectal foam experienced remission, resolution of rectal bleeding, and endoscopic improvement at week six (P < 0.05 for all comparisons in both trials) (Sandborn et al, 2015).

Oral vs. topical mesalamine

- A meta-analysis found combined oral and topical 5-ASA therapy to be superior to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Also, intermittent topical 5-ASA therapy was reported to be superior to oral 5-ASA therapy for preventing relapse of quiescent UC (Ford et al, 2012[a]).

Guidelines

- The Ulcerative Colitis Practice Guidelines in Adults from the American College of Gastroenterology (ACG) (2010) recommend oral mesalamine but do not differentiate between the different oral formulations available; a blanket recommendation for mesalamine is provided. All aminosalicylates are superior to placebo and equivalent to sulfasalazine in acute therapy of UC (Kornbluth et al, 2010). A guideline update is underway (ACG, 2017).
    - For the management of mild to moderate distal colitis, oral aminosalicylates, topical mesalamine, or topical corticosteroids are recommended (Evidence A [defined as High level of evidence; further research is very unlikely to change our confidence in the estimate of effect). Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical agents is “superior” to each agent used alone (Evidence A). Oral therapies effective for achieving and maintaining remission include balsalazide, mesalamine, olsalazine, and sulfasalazine. For the maintenance of remission in distal disease, mesalamine suppositories are effective for maintenance of remission in patients with proctitis, and mesalamine enemas are effective in patients with distal colitis (Evidence A). Balsalazide, mesalamine, and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone (Evidence A). Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission (Evidence A).
    - For the management of active mild to moderate extensive colitis, oral sulfasalazine or oral aminosalicylates in doses up to 4.8 g per day of the active 5-ASA moiety are considered first line (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates or patients who require rapid improvement (Evidence B [defined as Moderate level of evidence; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.]). For patients refractory to oral corticosteroids, 6-MP or azathioprine can be used for patients who are acutely ill, requiring intravenous therapy (Evidence A). Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. For maintenance of remission for mild to moderate extensive colitis, balsalazide, mesalamine, olsalazine, and sulfasalazine are effective in reducing the number of relapses (Evidence A). Azathioprine or 6-MP can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates (Evidence A). Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen (Evidence A).
    - For the management of severe colitis in a patient who is refractory to maximum oral treatment with aminosalicylates, oral prednisone, and topical medications, infliximab is a treatment option if urgent hospitalization is not required (Evidence A). Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown (Evidence A).
- The World Gastroenterology Organization Global Guidelines state that 5-ASA products are useful for treating both colitis flare-ups and maintenance of remission. A combination of oral with topical 5-ASA products is more effective than oral agents alone for induction of remission of mild to moderate UC. Rectal 5-ASA products are more beneficial than rectal corticosteroids in UC. Limited evidence exists for 5-ASA products in CD; these products are mainly used in patients who cannot tolerate corticosteroids. Corticosteroids provide rapid relief of symptoms by suppressing inflammation and should be used to induce remission; they have no role in maintenance of remission and side effects limit duration of use. Budesonide may have less adverse events than other corticosteroid options (Bernstein et al, 2015).
- The ACG recently released a clinical guideline addressing preventive care in IBD. According to published data, patients with IBD do not receive preventive care services at the same rate as general medical patients. Increased coordination between gastroenterology and primary care providers is recommended, as well as proper age-appropriate immunization, cervical and skin cancer screenings, depression and anxiety screening, and smoking cessation counseling for patients with CD (Farraye et al, 2017).

SAFETY SUMMARY

- Contraindications include hypersensitivity to salicylates or any component for the drugs in this class. AZULFIDINE EN-tabs are contraindicated in patients with intestinal or urinary obstruction or in patients with porphyria, as sulfonamides may precipitate an acute attack.
- Warnings include mesalamine acute intolerance syndrome, exacerbations of colitis, and caution using drugs in this class in patients with hepatic or renal impairment. Mesalamine products (LIALDA and PENTASA) and sulfasalazine products (AZULFIDINE and AZULFIDINE EN-tabs) may interfere with laboratory tests for normetanephrine. Rectal mesalamine may cause oligospermia and pancolitis.
- Due to the potential for severe blood dyscrasias, complete blood counts, including differential white cell count, and liver function tests should be performed before starting sulfasalazine therapy (AZULFIDINE and AZULFIDINE EN-tabs) and every second week during the first three months of therapy; tests should be repeated once monthly for three months, then once every three months, and as clinically indicated.
- Rectal budesonide may cause hypercorticism, adrenal axis suppression, and increased risk of infection.
- Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) with mesalamine products may increase the risk of nephrotoxicity; use with caution.
- Oral mesalamine and CANASA should not be used with 6-mercaptopurine and azathioprine due to decreased thiopurine metabolism; an increased risk of myelosuppression may result.
- In general, the inflammatory bowel agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Balsalazide	Capsule (COLAZAL): 750 mg Tablet (GIAZO): 1.1 g	Treatment of mildly to moderately active UC in patients ≥ 18 years of age: Capsule: 2,250 mg three times daily for up to eight to 12 weeks Treatment of mildly to moderately active UC in patients 5 to 17 years of age: Capsule: 750 or 2,250 mg three times daily for up to eight weeks Treatment of mildly to moderately active UC in males ages ≥ 18 years of age: Tablet: Three 1.1 g tablets twice daily with or without food for up to eight weeks.	Contents of capsules may be sprinkled on applesauce and/or chewed; teeth/tongue discoloration may occur. Tablets may be taken with or without food.
Budesonide	Extended release tablet (UCERIS): 9 mg Rectal foam (UCERIS): 2 mg/actuation	Induction of remission in adults with active, mild to moderate UC: extended release tablet (UCERIS): 9 mg orally once daily in the morning for up to eight weeks. Induction of remission in patients with active mild to moderate distal UC extending up to 40 cm from the anal verge: rectal foam (UCERIS) 1 metered dose administered rectally twice daily (morning and evening) for two weeks followed by 1 metered dose administered rectally once daily (evening) for four weeks.	Swallow tablet whole with water; tablets should not be chewed, crushed, or broken. Tablet may be taken with or without food. Patients should be advised to avoid the consumption of grapefruit juice with UCERIS. Before administering UCERIS rectal foam, patients should empty their

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			bowels. After administration before bedtime, patients should not empty bowels again until the next morning. UCERIS rectal foam contains flammable propellants. Patients should avoid fire, flame, and smoking during and immediately following administration.
Mesalamine	Controlled-release capsule (PENTASA): 250 mg 500 mg Delayed-release tablet:* 800 mg (ASACOL HD) 1.2 g (LIALDA) Delayed-release capsule: 400 mg (DELZICOL) Extended-release capsules (APRISO): 0.375 g Rectal suppository (CANASA): 1,000 mg Rectal enema (ROWASA; sfROWASA [sulfite-free formulation]): 4 g/60 mL unit	Induction of remission of mildly to moderately active UC: Controlled-release capsule (PENTASA): 1 g four times daily Induction of remission of active, mild to moderate UC: Delayed-release tablet (LIALDA): 2.4 or 4.8 g once daily with a meal Maintenance of remission of UC in adults: Delayed-release capsule (DELZICOL): 1.6 g daily divided into two to four doses Delayed-release tablet (LIALDA): 2.4 g once daily with a meal Extended-release capsules (APRISO): 1.5 g daily in the morning Treatment of mildly to moderately active UC: Controlled-release capsule (PENTASA): 1 g four times daily Delayed-release capsule (DELZICOL): 800 mg three times daily for six weeks Treatment of mildly to moderately active UC in pediatric patients ages 5 years and older: Delayed-release capsule (DELZICOL): Weight of 17 to 32 kg: daily dose of 36 to 71 mg/kg/day divided into two doses; max dose of 1.2 g per day Weight of 33 to 53 kg: daily dose of 37 to 61 mg/kg/day divided into two	PENTASA: Capsules may be opened and the entire contents sprinkled onto applesauce or yogurt. ASACOL HD: should not be cut, broken, or chewed; take on an empty stomach, at least 1 hour before and 2 hours after a meal DELZICOL: Capsules should not be cut, broken, or chewed; may be taken without regard to food; capsules may be opened for patients who are unable to swallow the capsules whole. Two DELZICOL 400 mg capsules have not been shown to be interchangeable or substitutable with one mesalamine 800 mg delayed release tablet. LIALDA: Take with a meal. CANASA, ROWASA, & sfROWASA: Product may cause staining of surfaces and fabrics; lubricating gel may be used to assist with insertion of suppositories.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		doses; max dose of 2 g per day Weight of 54 to 90 kg: daily dose of 27 to 44 mg/kg/day divided into two doses; max dose of 2.4 g per day Treatment of moderately active UC: Delayed-release tablet (ASACOL HD): 1,600 mg (two 800 mg tablets) three times daily for six weeks Treatment of mildly to moderately active ulcerative proctitis: Rectal suppository (CANASA): 1,000 mg at bedtime, retained for one to three hours (or longer if possible), for a treatment duration of three to six weeks Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis: Rectal enema (ROWASA; sfROWASA): 4 g (one enema) once daily at bedtime, retained for eight hours for three to six weeks based upon symptoms and sigmoidoscopic findings	
Olsalazine	Capsule (DIPENTUM): 250 mg	Maintenance of remission of UC in patients who are intolerant of sulfasalazine: Capsule: 1 g daily in two divided doses	
Sulfasalazine	Tablet (AZULFIDINE): 500 mg Delayed-release tablet (AZULFIDINE EN-tabs): 500 mg	Treatment of mild to moderate UC, and as adjunctive therapy in severe UC, and prolongation of the remission period between acute attacks of UC: Tablet and delayed-release tablet: initial, 3 to 4 g/day in divided doses with dosing intervals not exceeding eight hours; maintenance, 2 g/day Treatment of mild to moderate UC, and as adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC age 6 years and older: Tablet and delayed-release tablet: initial, 40 to 60 mg/kg/day divided into three to six doses; maintenance, 30 mg/kg/day divided into four doses If gastric intolerance occurs after the first few doses, reduce dose by half	Sulfasalazine products may cause an orange-yellow discoloration of the urine or skin. AZULFIDINE EN-tabs: swallow tablets whole.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		and slowly titrate over several days. If intolerance continues, stop drug for five to seven days, then re-introduce at a lower dose. Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs): Delayed-release tablet: 2 g daily in two evenly divided doses Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (ages 6 years and older): Delayed-release tablet: 30 to 50 mg/kg of body weight daily in two evenly divided doses; maximum dose, 2 g per day	

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Balsalazide	Capsule: No dosage adjustment required in the elderly; use with caution. Tablet: Monitor blood cell counts during therapy. Studies did not include sufficient numbers of elderly patients to determine if differences between younger and older patients exist.	Capsule: Approved for use in children 5 to 17 years of age. Tablet: Safety and efficacy in pediatric patients have not been established.	Use with caution in patients with a history of renal disease. Evaluate renal function prior to initiation of GIAZO therapy and periodically while on therapy.	Capsule: No dosage adjustment required. Tablet: Use caution and consider liver function testing when administering to patients with liver disease.	No adequate well-controlled studies of balsalazide have been completed in pregnant women. Use during pregnancy only if clearly needed. (COLAZAL) Pregnancy category B (GIAZO) Unknown whether excreted in breast milk; use with caution.
Budesonide (UCERIS tablet and rectal foam)	Insufficient data to determine if differences exist between younger	Safety and efficacy in pediatric patients have	No information	Monitor patients with moderate to severe hepatic	Pregnancy category C Excreted in breast

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	and older patients; use with caution.	not been established.		impairment for signs and/or symptoms of hypercorticism.	milk; Consider discontinuing nursing or drug.
Mesalamine (oral)	No dosage adjustment required in the elderly population; use with caution. Monitor complete blood counts in elderly periodically.	Safety and effectiveness in pediatric patients have not been established. DELZICOL: approved for use in pediatric patients 5 years of age and older	No dosage adjustment required; use with caution and monitor routinely. Evaluate renal function prior to initiation of APRISO and DELZICOL	No dosage adjustment required; use with caution.	Pregnancy category B (APRISO; DELZICOL; LIALDA; PENTASA) Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk (ASACOL HD) Mesalamine and its metabolite have been detected in breast milk; use with caution.
Mesalamine (rectal)	No dosage adjustment required in the elderly; use with caution. Monitor complete blood counts in elderly periodically. (CANASA)	Safety and efficacy in pediatric patients have not been established.	No dosage adjustment advised; use with caution. Evaluate renal function prior to initiation and periodically while using CANASA.	No dosage adjustment advised; use with caution.	Pregnancy category B Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk (CANASA) Mesalamine and its metabolite have been detected in breast milk; use with caution.
Olsalazine	No dosage adjustment required in the elderly; use with caution.	Safety and efficacy in pediatric patients have not been established.	Patients with impaired renal function should be monitored closely.	Patients with impaired hepatic function should be monitored closely.	Pregnancy category C Small amounts of active metabolite may pass into breast milk and cause diarrhea in infants; unless the benefit outweighs the risks, do not use in nursing women.
Sulfasalazine	No dosage adjustment	Safety and efficacy in	No dosage adjustment	No dosage adjustment	Pregnancy category B (AZULFIDINE)

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	required in the elderly; use with caution.	pediatric patients < 2 years with UC have not been established. FDA-approved for juvenile rheumatoid arthritis and UC for ages six years and older.	advised; use with caution.	advised; use with caution.	No adequate well-controlled studies of sulfasalazine have been completed in pregnant women. Excreted in breast milk; use caution. Insignificant amounts of un-cleaved sulfasalazine detected in breast milk; sulfapyridine levels are 30% to 60% of those in the maternal serum. Reports of bloody stools and/or diarrhea in infants fed breast milk from mothers on sulfasalazine. Monitor infant. Consider discontinuation of nursing or drug.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment goals of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations, and maintain remission from acute inflammation.
- For induction of remission of UC, no differences in efficacy or safety among the oral 5-ASA formulations are apparent (Wang et al, 2016[a]). Oral 5-ASA is similarly effective to sulfasalazine for induction of UC remission. For patients with mild to moderate UC, 2.4 g/day of oral 5-ASA is a safe and effective dose for inducing remission. Patients with moderate UC may benefit from 4.8 g/day of oral 5-ASA (Kornbluth et al, 2010).
- No overall differences in efficacy or safety among the oral 5-ASA formulations have been observed for the maintenance of UC remission, with all oral 5-ASA formulations being superior to placebo (Wang et al, 2016[b]). Sulfasalazine was shown to be superior to oral 5-ASA for maintenance of UC remission; however, when trials of 12 months duration or longer were evaluated, there was no longer a difference between sulfasalazine and 5-ASA. Once daily dosing and traditional dosing of oral 5-ASA regimens were similarly effective for maintenance of UC remission (Feagan and MacDonald, 2012; Feagan et al, 2013).
- Topical rectal therapies are the drugs of choice for distal disease and have been shown to be more effective than oral sulfasalazine therapy. In a meta-analysis, rectal 5-ASA therapy has been shown to be superior to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not superior to oral 5-ASA for symptomatic improvement or remission rates (Marshall et al, 2010). A smaller meta-analysis conducted in 2012 evaluating maintenance of symptomatic and endoscopic remission of UC, demonstrated that rectal 5-ASA was significantly superior to placebo over 12 months (Marshall et al, 2012). For maintenance of symptomatic and endoscopic remission of UC, rectal 5-ASA was not significantly different compared to oral 5-ASA. It has also been shown in clinical trials that topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent UC (Ford et

al, 2012[b]). Similarly, trials showed budesonide rectal foam was more effective than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis (Sandborn et al, 2015).

- According to the 2010 ACG guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine, and sulfasalazine (Kornbluth et al, 2010). Topical mesalamine agents are "superior" to topical steroids or oral aminosalicylates and the combination of oral and topical agents is "superior" to each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone.
- The 2010 ACG guidelines recognize sulfasalazine as a first-line agent in the management of mild to moderately active colitis, and note balsalazide, mesalamine, olsalazine, and sulfasalazine as effective therapies for reducing the number of relapses and the maintenance of mild to moderate disease remission (Kornbluth et al, 2010).
- The differences in drug therapies (i.e., pH-dependent parameters) allow for the tailoring of treatment based upon an individual's disease location and severity.
- Overall, oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine.

REFERENCES

- American College of Gastroenterology. Clinical Guidelines – Ulcerative Colitis in Adults. Available at: http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/. Accessed March 8, 2017.
- APRISO prescribing information. Salix Pharmaceuticals, Inc.; Raleigh, NC. June 2016.
- ASACOL HD prescribing information. Warner Chilcott, LLC; Rockaway, NJ. May 2016.
- AZULFIDINE EN-tabs prescribing information. Pfizer; New York, NY. June 2016.
- AZULFIDINE prescribing information. Pfizer; New York, NY. February 2014.
- Bernstein C, Eliakim A, Fedail S, et al. World Gastroenterology Organisation global guidelines on inflammatory bowel disease. Updated August 2015. Available at: http://www.worldgastroenterology.org/UserFiles/file/guidelines/inflammatory-bowel-disease-english-2015.pdf. Accessed March 8, 2017.
- CANASA prescribing information. Allergan USA, Inc. Irvine, CA. September 2016.
- Centers for Disease Control and Prevention (CDC). Epidemiology of the IBD. March 31, 2015. Available at: http://www.cdc.gov/ibd/ibd-epidemiology.htm. Accessed March 8, 2017.
- COLAZAL prescribing information. Salix Pharmaceuticals, Inc.; Bridgewater, NJ. June 2016.
- DELZICOL prescribing information. Warner Chilcott, Rockaway, NJ. March 2016.
- DIPENTUM prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. January 2014.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 8, 2017.
- Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. Am J Gastroenterol. 2017;112:241-58.
- Feagan BG, Chande N, MacDonald JK. Are there differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane Reviews. Inflamm Bowel Dis. 2013;19(9):2031-40.
- Feagan BG, MacDonald JK. Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis. Inflamm Bowel Dis. 2012;18:1785-1794.
- Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in UC: Systematic review and meta-analysis. Am J Gastroenterol. 2012[a];107:167-76.
- Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent UC: a meta-analysis. Clinical Gastroenterology and Hepatology. 2012[b];10:513-9.
- Geremia A, Biancheri P, Allan P, et al. Innate and adaptive immunity in inflammatory bowel disease. Autoimmun Rev. 2014 Jan;13(1):3-10.
- GIAZO prescribing information. Salix Pharmaceuticals, Inc., Morrisville, NC. June 2016.
- Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. UC practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23.
- LIALDA prescribing information. Shire US, Inc.; Wayne, PA. November 2015.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012, Issue 11. Art No.: CD004118. DOI: 10.1002/14651858.CD004118.pub2.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010, Issue 1. Art. No.: CD004115. DOI: 10.1002/14651858.CD004115.pub2.
- Micromedex Healthcare Series Web site. http://www.micromedexsolutions.com/home/dispatch. Accessed March 8, 2017.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). NIH Publication No. 14–1597. Ulcerative Colitis. September 2014. Available at: http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/. Accessed March 8, 2017.
- PENTASA prescribing information. Shire US, Inc.; Wayne, PA. October 2015.
- Peppercorn MA, Cheifetz AS. Definition, epidemiology, and risk factors in inflammatory bowel disease. UpToDate Web site[a]. www.uptodate.com. Accessed March 8, 2017.
- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. UpToDate Web site[b]. www.uptodate.com. Accessed March 8, 2017.
- ROWASA prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. June 2013.
- Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology. 2015;148(4):740-750.
- sfROWASA prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. June 2013.

- Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015, Issue 10. Art. No.: CD007698. DOI: 10.1002/14651858.CD007698.pub3.
- Tong JL, Huang ML, Xu XT, et al. Once-daily vs multiple-daily mesalamine for patients with ulcerative colitis: a meta-analysis. J Dig Dis. 2012;13:200-7.
- UCERIS extended-release tablet prescribing information. Salix Pharmaceuticals, Inc. Bridgewater, NJ. November 2016.
- UCERIS rectal foam prescribing information. Salix pharmaceuticals, Inc. Bridgewater, NJ. September 2016.
- Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016[a], Issue 4. Art. No.: CD000543. DOI: 10.1002/14651858.CD000543.pub4.
- Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016[b], Issue 5. Art. No.: CD000544. DOI: 10.1002/14651858.CD000544.pub4.
- Zhu Y, Ren-kuan T, Zhao P, et al. Can oral 5-aminosalicyclic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2012;24:487-494.

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OPTUMRx

Therapeutic Class Overview
Injectable Anticoagulants

INTRODUCTION

- Venous thromboembolism (VTE) can lead to significant health problems, which may become potentially fatal. It may occur in young, otherwise healthy adults, although it often occurs in patients who sustain multiple trauma(s), undergo major surgery, are immobile for a lengthy period of time, or have a hypercoagulable disorder (such as cancer). Due to clot formation within the venous circulation, VTE manifests as a stroke, deep vein thrombosis (DVT) and/or a pulmonary embolism (PE). The disease is often clinically silent, and death from PE can occur within minutes after the onset of symptoms, before treatment can be given (Blann et al, 2006).
- The estimated incidence of VTE is 300,000 to 600,000 annually. This estimate is considered to be an underestimate, however, due to missed or wrong diagnoses. The VTE incidence is similar or higher among African Americans and lower among Asian Americans and Native Americans. Most PE deaths are sudden and both DVTs and PEs are usually attributed to underlying disease (e.g., cancer, other chronic heart, lung, or renal disease). The 30-day VTE survival is 72% (DVT alone, 94.5%; PE with or without DVT, 55.6%) (Benjamin et al, 2017).
- Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, and chronic lower respiratory disease and injuries/accidents, in which more women die (approximately 60% of all US stroke deaths) from stroke every year than men. Each year, approximately 795,000 people experience a new or recurrent stroke. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage (ICH) strokes, and 3% are subarachnoid hemorrhage (SAH) strokes (Benjamin et al, 2017).
- The injectable anticoagulants include ARIXTRA®, FRAGMIN®, LOVENOX® and unfractionated heparin (UFH) and, in general, are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of VTE.
  - Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina (UA) and non-Q-wave MI.
  - Additional labeled indications for use of UFH include disseminated intravascular coagulation, prophylaxis and treatment of arterial embolism, and use in blood transfusions, extracorporeal circulation, and dialysis procedures. Heparin is also used as an anticoagulant for several other off-label indications.
- UFH is a mucopolysaccharide molecule that ranges in molecular weight from 3,000 to 30,000 daltons. Its primary effect as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of factors (F) IIa (thrombin), Xa, IXa, XIa, and XIIa (Garcia et al, 2012).
- FRAGMIN and LOVENOX are classified as low molecular weight heparins (LMWH) and exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including FXa and thrombin.
  - LMWH is a smaller fragment of UFH that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit FXa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this while the LMWH molecules typically are not (Hirsh et al, 2008; Weitz JI, 1997).
- Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable (Hirsh et al, 2008).
- ARIXTRA is a synthetic, selective FXa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-FXa activity is higher than that of the LMWH agents (Hirsh et al, 2008).
- Medispan class: Anticoagulants; Heparins and Heparinoid-like agents (intravenous [IV], inpatient-only formulations excluded.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ARIXTRA (fondaparinux)	Mylan	12/17/2001	✔
FRAGMIN (dalteparin)	Pfizer Inc	12/22/1994	-
HEPARIN SODIUM (unfractionated heparin)	Pfizer	Approved prior to Jan 1, 1982	✔
LOVENOX (enoxaparin)	Sanofi-Aventis US	03/29/1993	✔

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. The labeled indications for ARIXTRA, FRAGMIN, and LOVENOX are more specific than the labeled indications for UFH. However, UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI, and bridging in patients with atrial fibrillation (AF) and mechanical heart valves, by various guidelines.
- For most indications, UFH is administered IV; however, the subcutaneous (SC) route can be used for prophylaxis and/or treatment of VTE.
- Both LOVENOX and FRAGMIN are approved for prophylaxis of ischemic complications in UA and non-Q-wave MI.
- FRAGMIN is the only LMWH agent that is not approved for the treatment of acute VTE, yet it is the only agent in the class that is approved for the extended treatment of symptomatic VTE in patients with cancer.

Table 2. Food and Drug Administration Approved Indications

Indication	ARIXTRA (fondaparinux)	FRAGMIN (dalteparin)	HEPARIN SODIUM (unfractionated heparin)	LOVENOX (enoxaparin)
Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer		✔ ‖		
Prophylaxis of ischemic complications in UA and non-Q-wave MI		✔ ¶		✔ ¶
Treatment of acute DVT	✔ ‡			✔ **
Treatment of acute PE	✔ ‡			
Treatment of acute STEMI				✔ §
Prophylaxis and treatment of venous thrombosis and PE			✔	
Prophylaxis and treatment of thromboembolic complications associated with AF			✔	
Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation)			✔	
Prevention of clotting in arterial and cardiac surgery			✔	
Prophylaxis and treatment of peripheral arterial embolism			✔	
Anticoagulant use in blood transfusions, extracorporeal circulation, and dialysis procedures			✔	
Prophylaxis of DVT*				
Medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness		✔		✔
Patients undergoing abdominal surgery who are at risk for thromboembolic complications	✔	✔		✔
Patients undergoing hip fracture surgery	✔ †			
Patients undergoing hip replacement surgery	✔	✔		✔ #
Patients undergoing knee replacement surgery	✔			✔

‖In these patients therapy begins with the initial VTE treatment and continues for six months.
¶When concurrently administered with aspirin therapy.
*Which may lead to PE.
†Including extended prophylaxis.
#During and following hospitalization.
‡When administered in conjunction with warfarin.
**Indicated for inpatient treatment of acute DVT with or without PE, when administered in conjunction with warfarin, and for outpatient treatment of acute DVT without PE when administered in conjunction with warfarin.
§When administered in conjunction with warfarin when initial therapy is administered in the hospital.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent MI or death in patients with acute STEMI receiving thrombolysis and being managed medically or with percutaneous coronary intervention.

(Prescribing information: ARIXTRA, 2015; FRAGMIN, 2016; LOVENOX, 2013, HEPARIN SODIUM, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The evidence demonstrating the safety and efficacy of the injectable anticoagulants in FDA-approved indications is well established, and as mentioned previously, clinical guidelines support the use of these agents for these indications. Patients experiencing an acute coronary syndrome will generally receive treatment with an injectable anticoagulant in an acute hospital setting as recommended per current clinical guidelines (Levine et al 2011, O'Gara et al, 2013, Guyatt et al, 2012). When compared to UFH and placebo, LMWH was found to be superior or comparable to UFH treatment in patients with acute coronary syndrome.
- Currently, FRAGMIN is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing FRAGMIN to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with FRAGMIN at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow-up revealed a significant benefit in mortality with FRAGMIN in patients without known metastases of their cancer (Lee et al, 2003; Lee et al, 2005). The DALTECAN study found that the frequency of major bleeding events was lower during months 6 through 12 as compared to the first six months of FRAGMIN therapy in patients with cancer (Francis et al, 2015).
- An AHRQ Comparative Effectiveness Review found for the minority of patients at low or intermediate risk of recurrent ischemia, MI, or death, an initial conservative approach is recommended as LOVENOX reduced composite ischemic events and MI with mixed effects on bleeding when compared to UFH or ARIXTRA (Melloni et al, 2013).
- The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established. Several placebo-controlled trials, meta-analyses, and systematic reviews with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing orthopedic surgery have been conducted and consistently demonstrate their efficacy (Alikhan et al, 2003; Bergqvist et al, 1996; Bergqvist et al, 2002; Eriksson et al, 2003; Fuji et al, 2008; Hull et al, 2010; Lassen et al, 1998; Leizorovicz et al, 2004; Michot et al, 2002; Planes et al, 1996; Samama et al, 1999; Testroote et al, 2014; Torholm et al, 1991; Uchino et al, 2012; Anderson et al, 2013). When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis which include heparin, UFH, aspirin, and warfarin, "superiority" in terms of recurrent VTE and safety is not always consistent, which supports recommendations from current clinical guidelines (Andras et al, 2012; Bhutia et al, 2013; Colwell et al, 1994; Colwell et al, 1999; Cook et al, 2011; De et al, 2010; DeCarolis et al, 2012; Eriksson et al, 1991; Erkens et al, 2010; Ferres et al, 2011; Fitzgerald et al, 2001; Francis et al, 1997; Handoll et al, 2002; Kanaan et al, 2007; Kleber et al, 2003; Leclerc et al, 1996; McLeod et al, 2001; No authors listed, 1991; Othieno et al, 2007; Rasmussen et al, 2009; Salazar et al, 2010; Senaran et al, 2006; Anderson et al, 2013; Akl et al, 2014). For treatment and thromboprophylaxis in these patients, any of these options may be appropriate; however, LMWH or low-dose UFH are generally suggested in preference to the other agents recommended as alternatives (Guyatt et al, 2012). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (Robertson et al, 2017).
- Although data comparing the LMWH agents to ARIXTRA has not demonstrated significant "superiority" for one therapy in all outcomes, treatment with ARIXTRA appears to be associated with a lower incidence of VTE, and a comparable incidence of major bleeding compared to LOVENOX (Bauer et al, 2001; Eriksson et al, 2001; Lassen et al, 2002; Turpie et al, 2002b). In a meta-analysis of randomized-controlled trials comparing ARIXTRA to LMWH therapy (LOVENOX), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with ARIXTRA (Turpie et al, 2002a). Another trial noted no difference between ARIXTRA and FRAGMIN for the incidence of VTE and major bleeding (Agnelli et al, 2005).
- In general, recommendations from other clinical guidelines for other populations are in line with the American College of Chest Physicians (ACCP) guidelines (AAOS, 2011; Amsterdam et al, 2014; Levine et al, 2011; Kernan et al, 2014; Guyatt et al, 2012; Jaff et al, 2011; Bushnell et al, 2014; Lyman et al, 2015; O'Gara et al, 2013; January et al, 2014; Kernan et al, 2014). Treatment recommendations vary according to the indication.
    - For orthopedic (e.g., total hip or knee replacement) surgery, the American Academy of Orthopedic Surgeons (AAOS) does not recommend a specific medication (AAOS, 2011). The ACCP does favor LMWH over ARIXTRA, ELIQUIS, XARELTO, or UFH (Guyatt et al, 2012).
    - For non-orthopedic (e.g., general and abdominal-pelvic surgery) surgical patients requiring thromboprophylaxis who are at moderate to high risk for VTE and who are not at high risk for bleeding complications, LMWH and low dose UFH are both recommended as options (Guyatt et al, 2012).

- In patients with UA, NSTEMI, or STEMI, the American College of Cardiology (ACC) recommends anticoagulant therapy for a minimum of 48 hours and up to 8 days or until revascularization is performed in patients undergoing reperfusion. The recommended treatment options include UFH, LOVENOX and ARIXTRA (O'Gara et al, 2013; Kernan et al, 2014). For those patients undergoing PCI, LOVENOX, ARIXTRA, or UFH are recommended by most reputable guidelines. However, ARIXTRA should not be used as the sole anticoagulant administered due to risk of catheter thrombosis (Amsterdam et al, 2014; Levine et al, 2011). Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures or for various procedures (January et al, 2014).
- In acutely ill hospitalized (i.e., non-surgical) patients at increased risk of thrombosis, LMWH, low dose UFH, and ARIXTRA are recommended (Guyatt et al, 2012).
- For acute VTE (e.g., DVT or PE), LMWH or ARIXTRA is preferred over UFH (Guyatt et al, 2012; Lyman et al, 2015). For chronic management of VTE in patients with cancer, the American Society of Clinical Oncology (ASCO) guideline recommends LMWH for the initial six months due to its improved efficacy over warfarin. The guideline states that warfarin is an acceptable alternative for long-term therapy if LMWH is not readily available (Lyman et al, 2015). The most recent ACCP guidelines recommend PRADAXA (dabigatran), XARELTO (rivaroxaban), ELIQUIS (apixaban), or SAVAYSA (edoxaban) over warfarin for long-term VTE therapy (Kearon et al, 2016). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer. In patients with a VTE recurrence while on warfarin, PRADAXA, XARELTO, ELIQUIS, or SAVAYSA, treatment with a LMWH is recommended. Duration of anticoagulation after treatment of an acute thromboembolic event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor, and if it was the first or second thromboembolic event (Guyatt et al, 2012).
- In general, pregnant women and women who are breast-feeding with a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use UFH, or LMWH (Bushnell et al, 2014; Kernan et al, 2014).
- Patients with mechanical heart valves, AF, or VTE at high risk of developing thromboembolism, whose oral anticoagulation therapy is to be interrupted prior to an invasive procedure, would require bridging therapy with LMWH or UFH. Providers need to carefully consider risks and benefits of bridging in patients with the above mentioned conditions and moderate risk for thromboembolism. No bridging is indicated for patients at low risk for thromboembolism (Douketis et al, 2012; Douketis et al, 2015; Clark et al 2015).

SAFETY SUMMARY

- A boxed warning exists for the injectable anticoagulants (e.g., ARIXTRA, FRAGMIN, and LOVENOX) warning of spinal or epidural hematomas when anticoagulated with LMWH or heparinoids and in patients who are receiving neuraxial anesthesia or undergoing spinal puncture. Optimal timing between the administration of ARIXTRA, FRAGMIN or LOVENOX and neuraxial procedures is not known.
- The injectable anticoagulants (e.g., ARIXTRA, FRAGMIN, and LOVENOX) are contraindicated with major active bleeding. These agents are associated with an increased risk of bleeding and hemorrhage; therefore, use with caution in conditions with increased risk of hemorrhage. In addition, thrombocytopenia can occur with these agents.
- UFH is contraindicated in patients with a history of heparin-induced thrombocytopenia and thrombosis or a history of hypersensitivity to heparin or pork products. Although major active bleeding is not contraindicated, it is a warning to avoid heparin in the presence of major bleeding unless the benefit outweighs the risk.
- All injectable anticoagulants warn of drug interactions with medications that may enhance the risk of hemorrhage, which should be discontinued prior to initiation of therapy with any of the injectable anticoagulants, unless these medications are essential. However, in clinical trials, ARIXTRA in combination with oral anticoagulants, platelet inhibitors, nonsteroidal anti-inflammatory drugs, and digoxin did not significantly affect the pharmacokinetics and pharmacodynamics of any of the medications.
- Adverse reactions associated with agents in class include:
  - Injection site reaction, rash, and fever as adverse events commonly observed; and serious adverse events include bleeding-related adverse events with ARIXTRA use.
  - Injection site reaction, pain, and hematomas as adverse events commonly observed; and serious adverse events include anaphylaxis, abnormal liver function tests, and those bleeding-related adverse events with FRAGMIN use.
  - Gastrointestinal reactions, abnormal liver function tests, fever, thrombocytopenia, and bleeding-related as adverse events commonly observed; and serious adverse events include AF, heart failure, dermatologic reactions, pneumonia, and those adverse events related to bleeding with LOVENOX use.

- Hemorrhage, thrombocytopenia, hypersensitivity, and local injection reactions with UFH use.

- In November 2013, the FDA recommended that health care professionals consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as LOVENOX, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. New timing recommendations, which can decrease the risk of epidural or spinal hematoma, were added to the labels of LMWHs.

DOSING AND ADMINISTRATION

- FRAGMIN is administered via SC injection, and should not be administered via intramuscular injection. Routine coagulation tests such as Prothrombin Time and Activated Partial Thromboplastin Time are relatively insensitive measures of FRAGMIN activity; therefore, these measurements are unsuitable for monitoring the anticoagulant effect of FRAGMIN. In addition, in patients receiving FRAGMIN who experience platelet counts between 50,000 and 100,000/mm^3, the daily dose should be reduced by 2,500 international units until the platelet count recovers to ≥ 100,000/mm^3. In patients receiving FRAGMIN who experience platelet counts < 50,000/mm^3, discontinue treatment until the platelet count returns to > 50,000/mm^3.
- ARIXTRA is to be administered via SC injection only. Routine coagulation tests such as Prothrombin Time and Activated Partial Thromboplastin Time are relatively insensitive measures of ARIXTRA activity; therefore, these measurements are unsuitable for monitoring the anticoagulant effect of ARIXTRA. The anti-FXA activity can be measured. ARIXTRA should be discontinued if the platelet count is < 100,000/mm^3.
- LOVENOX can be administered via SC injection or intravenously, and should not be administered via intramuscular injection. All patients should be evaluated for a bleeding disorder before receiving LOVENOX, unless the medication is needed urgently. Coagulation parameters are also unsuitable for monitoring LOVENOX activity; therefore, routine monitoring of coagulation parameters is not required. LOVENOX should be discontinued if the platelet count is < 100,000/mm^3.
- UFH can be administered via SC injection or IV, and should not be administered via intramuscular injection. When using full-dose heparin, activated partial thromboplastin time (aPTT) should be monitored to aid in dose adjustments. Additionally, platelet counts may need to be monitored regularly depending on the patient's risk of heparin-induced thrombocytopenia. UFH should be discontinued if the platelet count is < 100,000/mm^3 or if thrombosis occurs.

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
ARIXTRA (fondaparinux)	Injection: 2.5 mg/0.5 mL 5 mg/0.4 mL 7.5 mg/0.6 mL 10 mg/0.8 mL	Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)* Prophylaxis of DVT in patients undergoing hip fracture surgery: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)†; an extended prophylaxis course of up to 24 additional days is recommended‡ Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)† Prophylaxis of DVT in patients undergoing knee replacement surgery: Injection: 2.5 mg SC once-daily after hemostasis has been	Do not mix other medications or solutions with ARIXTRA.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)† Treatment of acute DVT: Injection: 5 (< 50 kg), 7.5 (50 to 100 kg) or 10 (> 100 kg) mg SC once-daily for ≥ 5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)§ Treatment of acute PE: Injection: 5 (< 50 kg), 7.5 (50 to 100 kg) or 10 (> 100 kg) mg SC once-daily for ≥ 5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)§	
FRAGMIN (dalteparin)	Injection: 2,500 IU/0.2 mL 5,000 IU/0.2 mL 7,500 IU/0.3 mL 10,000 IU/1 mL 12,500 IU/ 0.5 mL 15,000 IU/ 0.6 mL 18,000 IU/ 0.72 mL 95,000 IU/ 3.8 mL	Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer: Injection: initial, 200 IU/kg SC once-daily for 30 days; maintenance, approximately 150 IU/kg SC once-daily during months two through six; maximum, daily doses should not exceed 18,000 IU Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 120 IU/kg, but not more than 10,000 IU, SC every 12 hours; maintenance, continue treatment until the patient is clinically stabilized (usual duration, five to eight days) Prophylaxis of DVT in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness: Injection: 5,000 IU SC once-daily‖ Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: preoperatively, 2,500 IU SC once-daily one to two hours prior to surgery; postoperatively, 2,500 IU SC once-daily (usual duration, five to 10 days) In patients undergoing abdominal surgery with a high risk of thromboembolic complications, the recommended dose of dalteparin is 5,000 IU SC the evening before the surgery, then 5,000 IU SC once-daily postoperatively (usual duration, five to 10 days); alternatively, patients with malignancy can administer 2,500 IU SC one to two hours prior to surgery, followed by 2,500 IU SC 12 hours later, then 5,000 IU SC once-daily (usual duration, five to 10 days) Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: preoperatively, 5,000 IU SC 10 to 14 hours before surgery or 2,500 IU SC within two hours before surgery; postoperatively, 2,500 to 5,000 IU SC four to eight hours after surgery plus 5,000 IU SC once daily (usual duration, five to 10	Dosage reductions may be required in patients with cancer and acute symptomatic VTE who develop thrombocytopenia. FRAGMIN should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		days after surgery)¶	
HEPARIN SODIUM (unfractionated heparin)	Preservative-free injection (1,000 USP units/mL): 2,000 USP units/2 mL Injection (contains benzyl alcohol) (1,000 USP units/mL): 10,000 USP units/10 mL 30,000 USP units/30 mL (5,000 USP units/mL): 50,000 USP units/10 mL 5,000 USP units/mL (10,000 USP units/mL): 10,000 USP units/mL	Therapeutic anticoagulant effect with full-dose heparin *SC injection:* 333 units/kg initially followed by 250 units/kg every 12 hours *Intermittent IV injection*: 10,000 units initially followed by 5000 to 10,000 units every 4 to 6 hours *Continuous IV infusion*: 5000 units initially followed by 20,000 to 40,000 units per 24 hours Pediatric use Initial dose: 75 to 100 units/kg (IV bolus over 10 minutes) Maintenance dose: Infants: 25 to 30 units/kg/hour >1 year old: 18 to 20 units/kg/hour Cardiovascular surgery Minimum dose: 150 units/kg; higher doses of 300 units/kg is used for procedures that last 1 hour and 400 units/kg for procedures that last longer than 1 hour Low-dose prophylaxis of postoperative thromboembolism *SC injection:* 5000 units 2 hours before surgery and 5000 units every 8 to 12 hours for 7 days or until patient is ambulatory, whichever is longer Blood transfusion 400 to 600 USP units/100 mL of whole blood Extracorporeal dialysis 25 to 30 units/kg followed by 1500 to 2000 units/hour if specific manufacturers' recommendations are not available	Dosing recommendations are based on a 68 kg patient.
LOVENOX (enoxaparin)	Injection (100 mg/mL): 30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/1 mL 300 mg/3 mL Injection (150 mg/mL): 120 mg/0.8 mL 150 mg/1 mL	Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 1 mg/kg SC every 12 hours for a minimum of two days and continued until clinical stabilization (usual duration, two to eight days)# Injection (patients with creatinine clearance (CrCL) < 30 mL/minute): 1 mg/kg SC once-daily Prophylaxis of DVT in medical patients who are at risk of thromboembolic complications due to severely restricted mobility during acute illness: Injection: 40 mg SC once-daily (usual duration, six to 11 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications:	For IV administration, LOVENOX can be mixed with normal saline solution or 5% dextrose in water. For SC administration, LOVENOX should not be mixed with other injections or infusions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		Injection: preoperatively, 40 mg SC two hours prior to surgery; postoperatively, 40 mg SC once-daily (usual duration, seven to 10 days)†† Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Prophylaxis of DVT in patients undergoing hip replacement surgery:</u> Injection: initial, 30 mg SC 12 to 24 hours after surgery or 40 mg SC once-daily administered 12(±3) hours prior to surgery; maintenance, 40 mg SC once-daily for three weeks (usual duration, seven to 10 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Prophylaxis of DVT in patients undergoing knee replacement surgery:</u> Injection: initial, 30 mg SC 12 to 24 after surgery (usual duration, seven to 10 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Treatment of acute DVT:</u> Injection (outpatient): 1 mg/kg SC every 12 hours for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)‡‡ Injection (outpatients with CrCL < 30 mL/minute): 1 mg/kg SC once-daily Injection (inpatient): 1 mg/kg SC twice-daily or 1.5 mg/kg SC once daily both for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)‡‡ Injection (in patients with CrCL < 30 mL/minute): 1 mg/kg SC once-daily <u>Treatment of acute ST-segment elevation MI:</u> Injection: initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC twice-daily; maximum, 100 mg for the first two doses, followed by 1 mg/kg dosing for the remaining doses Injection (patients < 75 years of age with CrCL < 30 mL/minute): initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC once-daily Injection (patients ≥ 75 years of age with CrCL < 30 mL/minute): 1 mg/kg SC once-daily	

DVT=deep vein thrombosis, IU=international units, IV=intravenous, MI=myocardial infarction, PE=pulmonary embolism, SC=subcutaneous, UA=unstable angina, VTE=venous thromboembolism
*Up to 10 days of treatment have been administered in clinical trials.
†Up to 11 days of treatment have been administered in clinical trials.
‡A total of 32 days (perioperative and extended prophylaxis) was administered in clinical trials.
§Up to 26 days of treatment have been administered in clinical trials.
‖In clinical trials, the usual duration of administration was 12 to 14 days.
¶Up to 14 days of treatment have been well tolerated in clinical trials.
#Up to 12.5 days of treatment has been administered in clinical trials.
** Up to 14 days of treatment have been administered in clinical trials.
††Up to 12 days of treatment have been administered in clinical trials.
‡‡Up to 17 days of treatment have been administered in clinical trials.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ARIXTRA (fondaparinux)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Serious adverse events increase with age. Due to the risk of increased adverse events in renal impairment, use caution as renal function generally declines with age.	Safety and efficacy in children have not been established	Use caution in patients with a CrCL 30 to 50 mL/minute. Contraindicated in patients with a CrCL < 30 mL/minute.	No dosage adjustment required, however a higher incidence of hemorrhage was observed in patients with moderate impairment.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
FRAGMIN (dalteparin)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Due to the potential for an increased bleeding risk with increased age, use caution in older patients with low body weight, decreased renal function, and	Safety and efficacy in children have not been established Use caution with multiple-dose vials due to benzyl alcohol content	Renal dose adjustment is required; for CrCL < 30 mL/minute, monitor anti-Xa levels to determine the appropriate dose.	No dosage adjustment required.	Pregnancy Category B Minimally excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	concomitant medications.				
HEPARIN SODIUM (unfractionated heparin)	A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Lower doses may be required in these patients.	Although no adequate, well controlled studies have been conducted, pediatric dosing recommend-ations are based on clinical experience. The preservative-free formulation should be used in neonates and infants to avoid benzyl alcohol toxicity. Special attention should be given to ensure the correct strength of heparin is used to avoid fatal dosing errors.	Should be used with caution in severe renal disease due to an increased risk of hemorrhage.	Should be used with caution in liver disease with impaired hemostasis due to an increased risk of hemorrhage.	Pregnancy Category C Due to its high molecular weight, heparin is not likely to be excreted in human milk and would not be orally absorbed by the infant. Use caution when administering to a nursing mother and use the preservative-free formulation as benzyl alcohol is excreted in human milk and can be orally absorbed by the infant.
LOVENOX (enoxaparin)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established	No dosage adjustment for moderate renal dysfunction is required. Renal dose adjustment is required for severe renal dysfunction (CrCL < 30 mL/minute).	Not studied in hepatic dysfunction; use with caution.	Pregnancy Category B; does not increase risk of major developmental abnormalities; monitor for bleeding. Due to benzyl alcohol content and its ability to cross the placenta, use of the multiple-dose vial should be used with caution. Unknown whether excreted in breast milk; use with caution.

Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The injectable anticoagulants include UFH, LMWH agents (i.e., FRAGMIN, LOVENOX) and FXa inhibitors (i.e., ARIXTRA). The primary effect of UFH as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of FIIa (thrombin), Xa, IXa, XIa, and XIIa (Garcia et al, 2012). The FXa inhibitors and LMWH agents work by binding to antithrombin, causing inhibition of the clotting factors thrombin and FXa. These agents have a greater inhibitory effect on FXa compared to thrombin (Hirsh et al, 2008; Weitz et al, 1997).
- Because the LMWH agents are prepared using different methods of depolymerization, the various agents in this class differ and are not clinically interchangeable (Hirsh et al, 2008).
- Currently, ARIXTRA, UFH, and LOVENOX are available generically (Micromedex, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. Certain agents in the class are also FDA-approved for the treatment of acute STEMI or for prophylaxis of ischemic complications UA and non-Q-wave MI; however, treatment for these indications will most likely be initiated in an acute hospital setting.
- UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI and use during PCI, by various guidelines. For most indications, UFH is administered IV; however, the SC route can be used for prophylaxis and/or treatment of VTE. For prophylaxis, the SC dose is administered two or three times daily and for treatment, the SC dose is administered twice daily.
- Outpatient or inpatient administration of the injectable anticoagulants for prophylaxis and treatment of VTE may be appropriate depending on the specific clinical situation. The most recent ACCP guidelines recommend PRADAXA, XARELTO, ELIQUIS, or SAVAYSA over warfarin for long-term VTE therapy (Kearon et al, 2016). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer.
- Evidence from clinical trials and recommendations from clinical guidelines support the use of the injectable anticoagulants in FDA-approved indications.
- Several placebo-controlled trials have consistently demonstrated the efficacy of the injectable anticoagulants, but when compared to other methods of anticoagulation (e.g., heparin, rivaroxaban, UFH, warfarin), their superiority in terms of recurrent VTE and safety has not always been demonstrated (Alikhan et al, 2003; Andras et al, 2012; Bergqvist et al, 1996; Bergqvist et al, 2002; Brookenthal et al, 2001; Colwell et al, 1994; Colwell et al, 1999; Cook et al, 2013; De et al, 2010; Eriksson et al, 1991; Eriksson et al, 2008; Erkens et al, 2010; Fitzgerald et al, 2001; Francis et al, 1997; Fuji et al, 2008; Handoll et al, 2002; Hull et al, 2010; Kakkar et al, 2008; Kanaan et al, 2007; Bauersachs, 2010; Buller, 2012; Kleber et al, 2003; Anderson et al, 2013; Lassen et al, 1998; Lassen et al, 2008; Leclerc et al, 1996; Leizorovicz et al, 2004; McLeod et al, 2001; Michot et al, 2002; No authors listed, 1991; Othieno et al, 2007; Planes et al, 1996; Rasmussen et al, 2009; Salazar et al, 2010; Samama et al, 1999; Senaran et al, 2006; Torholm et al, 1991; Turpie et al, 2009; Uchino et al, 2012; Melloni et al, 2013; van der Heijden, 2001; Akl et al, 2014). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (Robertson et al, 2017).
- When comparing ARIXTRA to the LMWH agents, treatment with ARIXTRA has demonstrated superiority in terms of the incidence of VTE in the majority of clinical trials, while demonstrating a comparable rate of major bleeding (Agnelli et al, 2005; Bauer et al, 2001; Bauer et al, 2002; Eriksson et al, 2001; Eriksson et al, 2003; Lassen et al, 2002; Turpie et al, 2002; Turpie AG et al, 2002). However, data from two clinical trials revealed no difference between treatment with ARIXTRA compared to FRAGMIN and LOVENOX in the development of VTE (Eriksson et al, 2003; Turpie et al, 2002).
- One trial revealed no difference between FRAGMIN compared to UFH treatment in critically ill patients in decreasing the incidence of proximal DVT; however, the trial found a statistically lower incidence of PE (definite or probable) with FRAGMIN. This result did require a large number needed to treat of 111 patients in order to achieve this outcome (Cook et al, 2011).
- In terms of safety measures, one trial comparing patients who were given LOVENOX with moderate renal impairment to those with normal renal function resulted in significantly more major bleeds in patients with moderate renal impairment (DeCarolis et al, 2012). In women who met criteria for thromboprophylaxis (patients at high-risk for VTE) after cesarean, one study resulted in a greater proportion of women who had wound separation when given LOVENOX compared to those women who were not given LOVENOX (Ferres et al, 2011).

Table 5. Advantages and Disadvantages of Injectable Anticoagulants

Drug	Advantages	Disadvantages
ARIXTRA (fondaparinux)	May be used acutely for certain patients. May be used as alternative treatment in cases of heparin-induced thrombocytopenia (HIT).	Long half-life of 17 to 21 hours, which should be taken in account if managing a pre-operative patient. Not indicated in patients with symptomatic VTE and cancer or as prophylaxis of ischemic complications in UA and MI. No antidote effect Contraindicated in patients with severe renal impairment.
FRAGMIN (dalteparin)	Shorter half-life of 7 hours. Only agent approved for the extended treatment of symptomatic VTE in patients with cancer.	Not indicated in acute VTE or acute MI. Requires renal dose adjustment Partial antidote effect
HEPARIN SODIUM (unfractionated heparin)	Shortest half-life of 1 hour and therefore, can be reversed quickly No renal excretion Complete antidote effect	SC dosing is two to three times daily and not typically administered at home Most indications are for IV administration Most common cause of heparin-induced thrombocytopenia
LOVENOX (enoxaparin)	Shorter half-life of 7 hours. May be used acutely for certain patients.	Not FDA-approved specifically in cancer patients, although often prescribed. Requires renal dose adjustment Partial antidote effect

(Hilal-Dandan et al, 2014; Baroletti et al, 2006)

REFERENCES

- Agnelli G, Bergqvist D, Cohen AT, et al. Randomized clinical trial of postoperative fondaparinux vs perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212-1220.
- Akl EA, Kahale L, Barba M, [a] et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev. 2014 Jul 8;7:CD006650. doi: 10.1002/14651858.CD006650.pub4
- Alikhan R, Cohen AT, Combe S, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. Blood Coagul Fibrinolysis. 2003;14:341-346.
- American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report. 2011. Available at: http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf. Accessed March 6, 2017.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23; 130(25):e344-426.
- Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low molecular weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med. Jun 4, 2013;158(11):800-806.
- Andras A, Sala Tenna A, Crawford F. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2012: Issue 10. Art. No.: CD002001. DOI: 10.1002/14651858.CD002001.pub2.
- ARIXTRA prescribing information. Mylan Institutional LLC. Rockford, IL. October 2015.
- Baroletti SA, Golhaber SZ. Heparin-induced thrombocytopenia. Circulation. 2006;114(8):e355-e356.
- Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-1310.
- Bauersachs R, Berkowitz ST, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. NEJM. 2010;363:2499-2510.
- Benjamin E, Blaha MJ, et al. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. [Epub ahead of print]. Circulation. 2017 Jan 25. pii: CIR.0000000000000485. doi: 10.1161/CIR.0000000000000485.
- Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975-980.

- Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.
- Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2013: Issue 7. Art. No.: CD003074. DOI: 10.1002/14651858.CD003074.pub3.
- Blann AD, Lip GY. Venous thromboembolism. BMJ. 2006;332: 215–219.
- Brookenthal KR, Freedman KB, Lotke PA, et al. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. J Arthroplasty. 2001;16(3):293-300.
- Büller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-1297.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45(5):1545-88.
- Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. JAMA Intern Med. 2015;175(7):1163-1168.
- Colwell CW, Collis DK, Paulson R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am. 1999;81:932-940.
- Colwell CW, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 1994;76:3-14.
- Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients (PROTECT investigators). N Engl J Med. 2011 Apr 7;364(14):1305-1314.
- De A, Roy P, Garg VK, et al. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. Blood Coagul Fibrinolysis. 2010;21:57-61.
- DeCarolis DD, Thorson JG, Clairmont MA, et al. Enoxaparin Outcomes in Patients with Moderate Renal Impairment. Arch Intern Med 2012 Dec 10;172(22):1713.
- Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging in patients with atrial fibrillation. N Engl J Med. 2015;373:823-833.
- Douketis JD, Spyropoulos AC, Spencer FA, et al. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012; 141(2)(Suppl):e326S–e350S.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 7, 2017
- Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared to enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-1304.
- Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-2775.
- Eriksson BI, Kalebo P, Anthymyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. J Bone Joint Surg Am. 1991;73:484-493.
- Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery. A multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2003;163:1337-1342.
- Erkens PMG, Prins MH. Fixed dose subcutaneous low molecular weight heparins vs adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database of Systematic Reviews. 2010, Issue 9. Art. No.:CD001100. DOI:10.1002/14651858.CD001100.pub3.
- FDA. Low Molecular Weight Heparins: Drug Safety Communication – Recommendations to Decrease Risk of Spinal Column Bleeding and Paralysis. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. November 6, 2013. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm373918.htm. Accessed March 7, 2017.
- FDA approves first generic enoxaparin sodium injection [press release on the Internet]. Rockville (MD): Food and Drug Administration (US); 2010 Jul 23. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm. Accessed March 7, 2017.
- Ferres MA, Olivarez SA, Trinh V, et al. Rate of Wound Complications With Enoxaparin Use Among Women at High Risk for Postpartum Thrombosis. Obstet Gynecol 2011 Jan;117(1):119.
- FRAGMIN prescribing information. Pfizer, Inc. New York, NY. August 2016.
- Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study. J Thromb Haemost 2015; 13: 1028–1035.
- Francis CW, Pellegrini VD, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am. 1997;79:1365-1372.
- Fitzgerald RH, Spiro TE, Trowbridge AA, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am. 2001;83:900-906.
- Fuji T, Ochi T, Niwa S, et al. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci. 2008;13:442-451.
- Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e24S-e43S.
- Guyatt GH, Akl EA, Crowther M, et al. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(Suppl 2):7-47.
- Handoll HHG, Farrar MJ, McBirnie J, et al. Heparin, low molecular weight heparin and physical methods for preventing vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database of Systematic Reviews. 2002, Issue 4. Art. No.:CD000305. DOI:10.1002/14651858.CD000305.
- HEPARIN SODIUM prescribing information. Hospira, Inc. Lake Forest, IL. September 2016.
- Hilal-Dandan R, Brunton LL. Blood coagulation and Anticoagulant, fibrinolytic, and antiplatelet drugs. In: Hilal-Dandan R, Brunton LL. eds. Goodman and Gilman's Manual of Pharmacology and Therapeutics, 2nd ed. New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1810&sectionid=124493032. Accessed March 07, 2017.
- Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133 (Suppl 6):141S-159S.

- Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility. Ann Intern Med. 2010;153:8-18.
- Jaff MR, McMurtry MS, Archer SL, et al. On behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011 Apr 26;123(16):1788-1830.
- January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary. Circulation. 2014 Dec;130(23):2071-104.
- Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban vs short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial. Lancet. 2008 Jul 5;372(9632):31-39.
- Kanaan AO, Silva MA, Donovan JL, et al. Meta-analysis of venous thromboembolism prophylaxis in medically ill patients. Clin Ther. 2007;29(11):2395-2405.
- Kearon C, Aki EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315-352.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45:2160-2236.
- Kleber FX, Witt C, Vogel G, et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J. 2003;145:614-621.
- Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2776-2786.
- Lassen MR, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux vs preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomized double-blind comparison. Lancet. 2002;359:1715-1720.
- Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) after total hip arthroplasty-The Danish Prolonged Prophylaxis (DaPP) Study. Throm Res. 1998;89:281-287.
- Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med. 1996;124:619-626.
- Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin vs a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-153.
- Lee AYY, Rickles FR, Julian JA, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol. 2005;23:2123-2129.
- Leizorovicz A, Cohen AT, Turpie AGG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-879.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. J Am Coll Cardiol. 2011 Dec 6;58(24):e44-122.
- LOVENOX prescribing information. Sanofi-aventis, LLC. Bridgewater, NJ. November 2013.
- Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015; 33(6):654-656.
- McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin vs low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Ann Surg. 2001;233(3):438-444.
- Melloni C, Jones WS, Washam JB, et al. Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non-ST Elevation Myocardial Infarction. Rockville MD: Agency for Healthcare Research and Quality; Nov 2013. Report No: 13(14)-EHC125-EF.
- Michot M, Conen D, Holtz D, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low-molecular weight heparin. Arthroscopy. 2002;18(3):257-263.
- Micromedex Solutions [database on the Internet]. Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed March 7, 2017.
- No authors listed. Low-molecular-weight heparin (enoxaparin) vs dextran 70. The prevention of postoperative deep vein thrombosis after total hip replacement. Arch Intern Med. 1991;151:1621-1624.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127 doi: 10.1161/CIR.0b013e3182742c84.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 7, 2017.
- Othieno R, Abu Affan M, Okpo E. Home vs in-patient treatment for deep vein thrombosis. Cochrane Database of Systematic Reviews. 2007, Issue 3. Art. No.:CD003076. DOI:10.10002/14651858.CD003076.pub2.
- Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomized comparison of enoxaparin vs placebo. Lancet. 1996;348:224-228.
- Rasmussen MS, Jorgensen LN, Willie-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database of Systematic Reviews. 2009, Issue 1. Art. No.: CD004318. DOI:10.1002/14651858.CD004318.pub2.
- Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2017 Feb;2:CD001100. DOI: 10.1002/14651858.CD001100.pub4.
- Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors vs vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. Cochrane Database of Systematic Reviews. 2010, Issue 4. Art. No.:CD005981. DOI:10.1002/14651858.CD005981.pub2.
- Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793-800.
- Senaran H, Acaroglu E, Ozdemir HM, et al. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. Arch Orthop Trauma Surg. 2006;126:1-5.

- Testroote M, Stigter WAH, Janssen L, et al. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane Database of Systematic Reviews. 2014, Issue 4. Art. No.:CD006681. DOI:10.1002/14651858.CD006681.pub3.
- Torholm C, Broeng L, Seest Jorgensen P, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. J Bone Joint Surg (Br). 1991;73-B:434-438.
- Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: q meta-analysis of 4 randomized double-blind studies. Arch Intern Med. 2002a;162:1833-1840.
- Turpie AG, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux vs postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomized double-blind trial. Lancet. 2002;359:1721-1726.
- Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. Lancet. 2009 May 16;373(9676):1673-1680.
- Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172(5):397-402.
- van der Heijden JF, Hutten BA, Buller HR, et al. Vitamin K antagonists or low-molecular-weight heparin for the long term management of symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2001, Issue 3. Art. No.:CD002001. DOI:10.1002/14651858.CD002001.
- Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-698.

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Therapeutic Class Overview
Biguanides

INTRODUCTION

- Diabetes mellitus affects more than 29 million people in the U.S. About 86 million American adults have prediabetes, with 90% of this population unaware that they have the disease (CDC, 2016).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, and is characterized by elevated fasting and postprandial glucose concentrations (American Diabetes Association [ADA], 2016[a]). It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (ADA, 2016[b]).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the U.S. (CDC, 2016).
- More than 20% of health care spending is for people with diagnosed diabetes (CDC, 2016).
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy (Garber et al, 2017).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both; decreasing the rate of carbohydrate absorption; and blocking glucose reabsorption by the kidney (Inzucchi et al, 2015).
- Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin (ADA, 2017[b]).
- Metformin, the sole biguanide, is thought to have several mechanisms of action. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged (GLUCOPHAGE prescribing information, 2009).
- Metformin is also used off-label for management of women with polycystic ovarian syndrome (PCOS), a condition that affects about 6 to 7% of women in the reproductive age group (DynaMed 2017; Legro et al, 2013).
- Although metformin is the sole biguanide in the class, it is available in various dosage forms including tablets, several forms of extended-release tablets, and an oral solution. This review includes the single-ingredient metformin products. Metformin is also available in combination products with several other classes of antihyperglycemic drugs; however, the combination products are not included in this review.
- Medispan class: Biguanides

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
GLUCOPHAGE® (metformin tablets)	Bristol Myers Squibb	03/03/1995	✔
GLUCOPHAGE® XR (metformin tablets, extended release)	Bristol Myers Squibb	10/13/2000	✔
FORTAMET® (metformin tablets, extended release)	Andrx Labs LLC	04/28/2004	✔
GLUMETZA® (metformin tablets, extended release)	Salix	06/03/2005	✔
RIOMET® (metformin oral solution)	Sun Pharm Inds LTD	09/11/2003	-

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	GLUCOPHAGE	GLUCOPHAGE XR	FORTAMET	GLUMETZA	RIOMET
Adjunct to diet and exercise to improve glycemic control in adults and children with T2DM	✔				✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM		✔	✔	✔	

(Prescribing Information: FORTAMET, 2012; GLUCOPHAGE/GLUCOPHAGE XR, 2017; GLUMETZA, 2016; RIOMET, 2014)

Information on indications, safety, and dosing has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The effectiveness of metformin in T2DM as monotherapy and in combination with other oral antidiabetic agents and/or insulin has been demonstrated through many clinical trials. Most trials evaluated a number of glycemic outcomes such as hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG). Other metabolic outcomes often reported were body weight, body mass index (BMI), effects on insulin secretion, and effects on lipid parameters. In a recently published JAMA opinion paper, however, the authors noted that results from recent cardiovascular outcomes trials of patients with T2DM are moving away from a glucocentric approach, since drugs that lower HbA1c to similar levels had different effects on patient outcomes. Furthermore, the diabetes field is moving away from its historical reliance on surrogate markers and toward studies that asses outcome such as heart disease and mortality to identify drugs that achieve the goals of diabetes care (Lipska and Krumholz, 2017).
- A number of trials have demonstrated the effectiveness of metformin compared to placebo (Douek et al, 2005; Jones et al, 2002; Kooy et al, 2009; Wulffele et al, 2002). More often, metformin has been studied in comparison to an alternative antihyperglycemic drug, either as monotherapy or in various combination regimens (Aschner et al, 2010; Bailey et al, 2010; Bosi et al, 2009; Cryer et al, 2005; Defronzo et al, 1995; Derosa et al, 2010; Fonseca et al, 2012; Gottschalk et al, 2007; Henry et al, 2012; Jadzinsky et al, 2009; Kahn et al, 2006; Lewin et al, 2007; Lund et al, 2009; Neutel et al, 2013; Pavo et al, 2003; Russell-Jones et al, 2012; Stewart et al, 2006; UKPDS Group, 1998; Weissman et al, 2005).

- A number of trials and analyses have evaluated cardiovascular and other diabetes outcomes (Boussageon et al, 2012; Hemmingsen et al, 2012; Johnson et al, 2005; Kooy et al, 2009; Lamanna et al, 2011; Saenz et al, 2005). Trial results have not always been in agreement for these outcomes. A landmark study often cited in the literature is UKPDS 34, which compared metformin therapy to conventional treatment (primarily diet alone) on diabetes-related cardiovascular and other clinical outcomes, diabetes-related death, and all-cause mortality in overweight patients with T2DM. The study demonstrated a significantly reduced risk of these three outcomes in the group treated with metformin. However, the investigators also evaluated the use of metformin when added to sulfonylurea compared to sulfonylurea alone, and found contrary results: patients treated with metformin had an increased risk of diabetes-related death and all-cause mortality (UKPDS Group, 1998).
- Since UKPDS 34 was published, several other studies and meta-analyses have sought to gather more information on cardiovascular and other patient-relevant outcomes. A retrospective trial compared metformin to sulfonylureas and their combination for a composite endpoint of fatal or nonfatal cardiovascular-related events, and the trial demonstrated that patients in the metformin monotherapy group had a lower risk of the composite cardiovascular endpoint compared to sulfonylurea monotherapy (Johnson et al, 2005). A meta-analysis evaluated metformin compared to non-pharmacologic and other pharmacologic interventions for T2DM, and it was concluded that metformin showed a significant benefit compared to chlorpropamide, glyburide, or insulin for all-cause mortality and for any diabetes-related outcome (a composite measure evaluating a large number of outcomes such as sudden death, myocardial infarction, heart failure, stroke, amputation, retinopathy, and blindness) (Saenz et al, 2005). However, a prospective study with a 4.3-year follow-up that compared insulin plus metformin to insulin plus placebo failed to demonstrate a significant benefit for metformin for a composite macrovascular and microvascular endpoint. In this trial, a small benefit was seen for metformin on an aggregate macrovascular endpoint, but this failed to be statistically significant after adjusting for changes in body weight (Kooy et al, 2009). Several more recent meta-analyses have failed to conclusively demonstrate a cardiovascular benefit with metformin (Boussageon et al, 2012; Hemmingsen et al, 2012; Lamanna et al, 2011). Some investigators noted that significant differences were found for some outcomes, but these differences did not persist when data from UKPDS 34 was excluded (Boussageon et al, 2012; Lamanna et al, 2011).
- In addition to these outcomes, a number of studies evaluated the use of different dosage forms of metformin. Metformin is available in several different formulations, which include metformin immediate-release tablets and solution, as well as three sustained-release formulations. Metformin solution was found to have an equivalent rate and extent of absorption as metformin immediate-release tablets (RIOMET prescribing information, 2014). Clinical studies reported comparable changes in HbA1c between the immediate-release formulations and sustained-release formulations (Fujioka et al, 2003; Schwartz et al, 2006).
- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy in the absence of specific contraindications (ADA, 2017[b]; Copeland et al, 2013; Garber et al, 2017; Inzucchi et al, 2015; Qaseem et al, 2017).
- Metformin is utilized to treat women with PCOS. The Endocrine Society guideline recommends using metformin in women with PCOS and T2DM or impaired glucose tolerance and as a second-line therapy in women with PCOS and menstrual irregularity who cannot tolerate hormonal contraceptives. Metformin has no benefit in improving hirsutism, acne, or infertility (Legro et al, 2013).
- Metformin was explored as a weight loss agent in an analysis that has shown its effectiveness. However, Canadian guidelines on the management of adults who are obese and overweight advise against use of metformin for this indication due to adverse events and trial designs with confounders (Canadian Task Force et al, 2015).

SAFETY SUMMARY

- Contraindications:
    - Renal disease or renal dysfunction (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance).
    - Severe renal impairment (estimated glomerular filtration rate [eGFR] below 30 mL/min/1.73 m^2).
    - Known hypersensitivity to metformin hydrochloride.
    - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Boxed warnings:

- Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. Post-marketing cases, including fatal cases, of lactic acidosis associated with metformin have been reported.
    - Reported cases have occurred primarily in diabetic patients with significant renal insufficiency.
    - The risk of lactic acidosis increases with increasing age (age ≥ 65 years), use of intravascular iodinated contrast agents or certain other interacting medications, surgery and other procedures that involve withholding food and fluids, hypoxic states (e.g., acute congestive heart failure, cardiovascular collapse [shock], acute myocardial infarction, sepsis), excessive alcohol intake, and hepatic impairment.
    - If acidosis is suspected, metformin should be discontinued and the patient hospitalized immediately.

- Warnings:
    - Hypoxic states: Cardiovascular collapse (shock), congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such events occur in patients on metformin, the drug should be promptly discontinued.
    - Alcohol intake: alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while taking metformin.
    - Vitamin B_{12} levels: Low vitamin B_{12} levels have been observed in some patients on metformin, possibly due to reduced B_{12} absorption. Annual monitoring of hematologic parameters is advised.
    - Impaired hepatic function: Avoid metformin in patients with clinical or laboratory evidence of hepatic disease.
    - Hypoglycemia: May occur with insufficient caloric intake, strenuous exercise or with other drugs that lower glucose.
- Adverse drug events:
    - The most common are gastrointestinal in nature: diarrhea, flatulence, nausea and vomiting.
- Drug Interactions:
    - Cationic drugs (e.g., amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interacting with metformin by competing for common renal tubular transport systems. Careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended.
    - Medications affecting glycemic control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid): The co-administered drug may lead to loss of glycemic control; thus the patient should be closely observed.
    - Carbonic anhydrase inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. The risk of lactic acidosis may increase.
    - Discontinue metformin either at the time of, or prior to, iodinated contrast imaging procedures in patients with eGFR between 30 and 60 mL/min/1.73 m^2, patients with a history of liver disease, alcoholism, or heart failure, or patients who will be administered intra-arterial iodinated contrast. Renal function should be re-evaluated 48 hours after the imaging procedure and metformin may be restarted if stable.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
GLUCOPHAGE (metformin	Tablet: 500 mg,	Adults: Usual starting dose is 500 mg twice daily or 850	Dosing is varied. Start at a low dose and	Give in divided doses with meals.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
tablets)	850 mg, 1,000 mg	mg once daily. Dose increases should be made in increments of 500 mg weekly or 850 mg every two weeks in divided doses. Patients can also be titrated from 500 mg twice daily to 850 mg twice daily after two weeks. Pediatrics (age 10 to 16 years): Usual starting dose is 500 mg twice a day. Dosage increases should be made in increments of 500 mg weekly.	escalate slowly. Maximum daily dose is 2,550 mg in adults and 2,000 mg in children 10 to 16 years of age.	
GLUCOPHAGE XR (metformin tablets, extended release)	Extended-release tablets: 500 mg, 750 mg	Usual starting dose is 500 mg daily. Dose increases should be made in increments of 500 mg weekly.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,000 mg in adults.	Give once daily with evening meal. Swallow whole, never crush or chew.
FORTAMET (metformin tablets, extended release)	Extended release tablets: 500 mg, 1,000 mg	Usual starting dose is 1,000 mg daily, although 500 mg may be used when clinically appropriate. Dose increases should be made in increments of 500 mg weekly.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,500 mg in adults.	Take with full glass of water once daily with evening meal. Do not cut, crush or chew.
GLUMETZA (metformin tablets, extended release)	Extended release tablets: 500 mg, 1,000 mg	Usual starting dose is 500 mg daily. Dose increases should be made in 500 mg increments every one to two weeks.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,000 mg in adults.	Give once daily with evening meal. Swallow whole, never split, crush or chew. For a missed dose, patients should not take two doses in one day but instead should resume their usual dose with the next scheduled dose.
RIOMET (metformin oral solution)	Oral solution: 500 mg/5 mL	Adults: Usual starting dose is 500 mg (5 mL) twice a day or 850 mg (8.5 mL) once a day. Dose increases should be made in increments of 500 mg (5 mL) weekly or 850 mg (8.5 mL) every two weeks. Patients can also be titrated from 500 mg (5 mL) twice a day to 850 mg (8.5 mL) twice a day after two weeks.	Dosing is varied. Start at a low dose and escalate slowly. Maximum daily dose is 2,550 mg (25.5 mL) in adults and 2,000 mg (20 mL) in children 10 to 16 years of age.	Give in divided doses with meals.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Pediatrics (age 10 to 16 years): Usual starting dose is 500 mg (5 mL) twice a day. Dosage increases should be made in increments of 500 mg (5 mL) weekly.		

SPECIAL POPULATIONS

Table 4 provides information on the use of metformin in special populations. A key distinction between products is that the safety and efficacy of metformin tablets and oral solution have been demonstrated in children 10 to 16 years of age, while this has not been demonstrated for metformin extended-release tablets.

- In April 2016, the Food and Drug Administration (FDA) issued a Drug Safety Communication requiring a change to metformin labeling in order to reflect that metformin may be safely used in patients with mild to moderate renal impairment (FDA, 2016). Changes have not yet been reflected in all the most recently revised labeling for each product; however, recommendations from the FDA have been incorporated in the GLUMETZA and GLUCOPHAGE prescribing information listed in Table 4. The FDA also recommended that a better estimate of renal function (i.e., eGFR) be used in place of blood creatinine as a measure of renal function.
- A systematic review evaluated glibenclamide (glyburide), metformin and insulin in 15 studies (N=2,509) for the treatment of gestational diabetes (Balsells et al, 2015). Glyburide was associated with higher birth weight, (7 studies; pooled mean difference 109 g; 95% CI, 35.9 to 181; P=0.003; I^2=0%) and more macrosomia (6 studies; pooled risk ratio 2.62; 95% CI, 1.35 to 5.08; P=0.004; I^2=34%) and neonatal hypoglycemia (7 studies; pooled risk ratio 2.04; 95% CI, 1.30 to 3.20; P=0.002; I^2=0%) compared to insulin. Compared to insulin, metformin was associated with lower maternal weight gain (4 studies; pooled mean difference -1.14 kg; 95% CI, -2.22 to -0.06; P=0.04; I^2=64%), lower gestational age at delivery (6 studies; pooled mean difference -0.16 weeks; 95% CI, -0.3 to -0.02; P=0.03; I^2=0%), and more preterm birth (5 studies; pooled risk ratio 1.5; 95% CI, 1.04 to 2.16; P=0.03; I^2=0%). In comparisons of metformin and glyburide, metformin was associated with lower maternal weight gain (1 study; pooled mean difference -2.06 kg; 95% CI, -3.98 to -0.14; P=0.04), less macrosomnia (2 studies; pooled risk ratio 0.33; 95% CI, 0.13 to 0.81; P=0.02; I^2=0%), and fewer large for gestational age newborns (1 study; pooled risk ratio 0.44; 95% CI, 0.21 to 0.92; P=0.03). Authors concluded that glyburide should not be used for the treatment of gestational diabetes, and metformin may be an oral option.
- A multicenter randomized controlled trial showed that metformin reduced progression to diabetes by 40% in women with a history of gestational diabetes mellitus over a 10 year period (Aroda et al, 2015).

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Metformin tablets (GLUCO-PHAGE) and oral solution (RIOMET)	Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Do not initiate in patients ≥80 years of age unless	Safety and efficacy have been established in pediatric patients ages 10 to 16 years.	Contraindicated in renal disease/ dysfunction as suggested by serum creatinine ≥1.5 mg/dL in males and ≥1.4 mg/dL in females or abnormal CrCL (RIOMET). Contraindicated in	Pharmacokinetic studies have not been conducted in patients with hepatic insufficiency. Because impaired hepatic function may limit the ability to clear lactate, metformin should	Pregnancy Category B; not recommended for use in pregnancy* Unknown. Excreted into milk in animal studies. A decision should be made to discontinue nursing or discontinue the

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	measurement of CrCL demonstrates that renal function is not reduced.		patients with eGFR < 30 mL/min/1.73 m^2. Discontinue if eGFR < 30 mL/min/1.73 m^2. Initiation not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2.	generally be avoided in patients with hepatic disease.	drug.
Metformin extended release tablets (FORTAMET, GLUCO-PHAGE XR)	See metformin tablets/oral solution.	Safety and effectiveness have not been established.	See metformin tablets/oral solution.	See metformin tablets/oral solution.	Pregnancy Category B; not recommended for use in pregnancy* See metformin tablets/oral solution.
Metformin extended release tablets (GLUMETZA)	Dosing in elderly should be cautious and usually start low. Renal function should be assessed more frequently.	Safety and effectiveness have not been established.	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Discontinue if eGFR < 30 mL/min/1.73 m^2. Initiation not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m^2. Assess benefit and risk of therapy in patients whose eGFR falls below 45 mL/min/1.73 m^2.	See metformin tablets/oral solution.	Pregnancy Category B; not recommended for use in pregnancy* Unknown. Excreted into milk in animal studies.

CrCL=creatinine clearance; eGFR=estimated glomerular filtration rate

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

CONCLUSION

- Metformin is a well-established medication for the treatment of T2DM. Treatment guidelines are consistent in their recommendation that metformin be considered a first-line treatment for T2DM in the absence of contraindications.
- Metformin has been shown to be effective as monotherapy, in combination with other oral antidiabetic agents, and in combination with insulin.
- Consistent benefits are seen with metformin for HbA1c and FPG. A large meta-analysis estimated the effect of metformin on HbA1c to be approximately 1.1% in monotherapy trials, 0.95% in trials adding metformin to other oral therapies, and 0.6% in trials adding metformin to insulin (Hirst et al, 2012).
- A benefit of metformin is its association with weight loss or maintenance, as opposed to several other antidiabetic drug categories associated with weight gain.

- Despite strong efficacy on metabolic outcomes in T2DM, data on cardiovascular outcomes and mortality have not consistently demonstrated a benefit with metformin.
- Metformin is used off-label as a second-line agent in women with PCOS and menstrual irregularities if they do not tolerate hormonal contraceptives (Legro et al, 2013).
- Metformin has a strong safety record when used according to guidelines. A main safety concern is lactic acidosis; the prescribing information reports post-marketing cases of metformin-associated lactic acidosis. However, a 2010 Cochrane Review including 347 studies failed to identify any cases of fatal or non-fatal lactic acidosis caused by metformin (Salpeter et al, 2010).
- The most common adverse effects associated with metformin are gastrointestinal (diarrhea and nausea/vomiting).
- Metformin is available in several dosage forms for dose individualization and patient convenience. Several products (GLUCOPHAGE, GLUCOPHAGE XR, GLUMETZA, and FORTAMET) are available generically, while RIOMET remains brand name only at this time.

REFERENCES

- American Diabetes Association [a]. Diabetes Basics: Type 2 (2016). Available at: http://www.diabetes.org/diabetes-basics/type-2/?loc=util-header_type2. Accessed March 13, 2017.
- American Diabetes Association [b]. Standards of Medical Care in Diabetes – 2017. Diabetes Care. 2017;40(suppl 1):S1-S135..
- Aroda VR, Christophi CA, Edelstein SL, et al for the Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the diabetes prevention program outcomes study 10-year follow up. J Clin Endocrinol Metab. 2015;100(4):1646-1653.
- Aschner P, Katzeff HL, Guo H, et al for the Sitagliptin Study 049 Group. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2010;12(3):252-261.
- Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;375(9733):2223-2233.
- Balsells M, Garcia-Patterson A, Sola I, et al. Glibenclamide, metformin and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ. 2015 Jan 21;350:h102.
- Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naïve patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism. 2009;11:506-515.
- Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med 2012;9(4):e1001204.
- Canadian Task Force on Preventative Health Care. Recommendations for prevention of weight gain and use of behavioural and pharmacologic interventions to manage overweight and obesity in adults in primary care. CMAJ. 2015;187(3):184-195.
- Centers for Disease Control and Prevention (CDC). At a glance 2016. Diabetes – working to reverse the US epidemic. Available at: https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/diabetes-aag.pdf. Accessed March 13, 2017.
- Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics. 2013;131(2):364-382.
- Cryer DR, Nicholas SP, Henry DH, et al. Comparative outcomes study of metformin intervention versus conventional approach. Diabetes Care. 2005 Mar;28(3):539-43.
- DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995 Aug;333(9):541-9.
- Derosa G, Maffioli P, Salvadeo SA, et al. Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. Metabolism. 2010 Jun;59(6):887-95.
- Douek IF, Allen SE, Ewings P, et al; the Metformin Trial Group. Continuing metformin when starting insulin in patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. Diabet Med. 2005 May;22(5):634-40.
- Drugs@FDA. U.S. Food and Drug Administration. 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 13, 2017.
- Fonseca V, Zhu T, Karyekar C, et al. Adding saxagliptin to extended-release metformin vs. uptitrating metformin dosage. Diabetes, Obesity and Metabolism. 2012;14(4):365-371.
- Food and Drug Administration (FDA). FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Silver Spring, MD: U.S. Department of Health and Human Services; 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed March 13, 2017.
- FORTAMET prescribing information. Shionogi Inc. Florham Park, NJ. April 2012.
- Fujioka K, Pans M, Joyal S. Glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. Clin Ther. 2003 Feb;25(2):515-29.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm -2017 executive summary. Endocr Pract. 2017;23(2):207-237. Available from: https://www.aace.com/sites/all/files/diabetes-algorithm-executive-summary.pdf. Accessed March 13, 2017.
- GLUCOPHAGE prescribing information. Bristol-Myers Squibb Company. Princeton, NJ. February 2017.
- GLUCOPHAGE XR prescribing information. Bristol-Myers Squibb Company. Princeton, NJ. February 2017.
- GLUMETZA prescribing information. Salix Pharmaceuticals. Bridgewater, NJ. April 2016.

- Gottschalk M, Danne T, Vlajnic A, et al. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes. Diabetes Care. 2007 Apr;30(4):790-4.
- Hemmingsen B, Christensen LL, Wetterslev J, et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012;344:e1771.
- Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. Int J Cln Pract. 2012;66(5):446-456.
- Hirst JA, Roberts NW, Farmer AJ, et al. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes Care. 2012;35:446-454.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;25:1364-1379.
- Jadzinsky M, Pfutzner A, Paz-Pacheco E, et al; CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared to either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009;11(6):611-22.
- Johnson JA, Simpson SH, Toth EL, et al. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med. 2005 Apr;22:497-502.
- Jones KL, Arslanian S, Peterokova VA, et al. Effect of metformin in pediatric patients with type 2 diabetes. Diabetes Care. 2002 Jan;25(1):89-94.
- Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Mar 29;355:2427-43.
- Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009;169(6):616-625.
- Lamanna C, Monami M, Marchionni N, et al. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2011;13:221-228.
- Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013; 98: 4565-4592.
- Lewin A, Lipetz R, Wu J, et al. Comparison of extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes: a multicenter, double-blind, randomized, controlled, phase III study. Clin Ther. 2007 May;29(5):844-55.
- Lipska KJ, Krumholz HM. Is Hemoglobin A1C the right outcome for studies of diabetes? JAMA 2017;317(10):1017-1018.
- Lund SS, Tarnow L, Frandsen M, et al. Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomized, double blind trial. BMJ. 2009;339:b4324.
- Neutel JM, Zhao C, Karyekar CS. Adding saxagliptin to metformin extended release (XR) or uptitration of metformin XR: efficacy on daily glucose measures. Diabetes Ther. 2013;4(2):269-283.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 13, 2017.
- Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003 Apr;88(4):1637-45.
- Polycystic ovary syndrome. In DynaMed [database online]. EBSCO Information Services. Available by subscription at: http://web.a.ebscohost.com/dynamed/detail?vid=3&sid=47e309f8-2b67-4adf-b986-49a91fa300f8%40sessionmgr4002&hid=4114&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#AN=116286&db=dme. Updated August 15, 2016. Accessed March 13, 2017.
- Qaseem A, Barry MJ, Humphrey LL, et al for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:279-290.
- RIOMET prescribing information. Ranbaxy Laboratories, Inc. Jacksonville, FL. April 2014.
- Russell-Jones D, Cuddihy RM, Hanefeld M, et al, on behalf of the DURATION-4 Study Group. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). Diabetes Care. 2012;35:252-258.
- Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002966.
- Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD002967. doi: 10.1002/14651858.CD002967.pub4
- Schwartz S, Fonseca V, Berner B, et al. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. Diabetes Care. 2006 Apr;29(4):759-64.
- Stewart MW, Cirkel DT, Furuseth K, et al. Effect of metformin plus rosiglitazone compared with metformin alone on glycemic control in well-controlled type 2 diabetes. Diabet Med. 2006;23:1069-78.
- UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
- Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE study. Curr Med Res Opin. 2005 Dec;21(12):2029-35.
- Wulffelé MG, Kooy A, Lehert P, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care. 2002 Dec;25(12):2133-40.

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Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects approximately 29.1 million people in the United States (U.S.), which is approximately 9.3% of the population (*American Diabetes Association [ADA] Diabetes Basics 2017*).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*ADA Diabetes Basics 2017*).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2017*).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, and lixisenatide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (Saxenda) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon (exenatide ER)	-
Byetta (exenatide)	-
Symlin (pramlintide)	-
Tanzeum (albiglutide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

(*DRUGS@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Symlin (pramlintide)	Tanzeum (albiglutide)	Trulicity (dulaglutide)	Victoza (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✔			
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✔			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✔	✔	✔		✔	✔	✔
Limitations of Use							
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔		✔	✔	✔
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔		✔	✔	✔
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔	✔	✔		✔	✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.					✔	✔	
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔						
Not studied in combination with prandial/short-acting insulin.	✔	✔			✔		✔
Use with insulin has not been studied and is not recommended.			✔				

(Prescribing information: *Adlyxin 2016*, *Bydureon 2017*, *Byetta 2015, Symlin 2016, Victoza 2016, Tanzeum 2016, Trulicity 2017*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Albiglutide

- The approval of albiglutide was based on 8 pivotal trials involving over 5000 patients as a part of the HARMONY phase 3 program (*Tanzeum FDA Medical Review 2014*, *Tanzeum Prescribing Information 2016*). The majority of the trials were multicenter (MC), randomized, double-blind (DB), placebo-controlled (PC) or active control (AC) studies in adult patients with inadequately controlled T2DM (HbA1c 7% to 10%); however, 3 trials were open-label (OL). The primary outcome in each trial was change in HbA1c from baseline at 26 to 104 weeks.
  - HARMONY 1 demonstrated that albiglutide 30 mg once weekly was superior to placebo in patients taking concurrent pioglitazone with or without metformin at 52 weeks, with a mean reduction in HbA1c of 0.8% (*Reusch et al 2014*).
  - HARMONY 2 compared both albiglutide 30 mg and 50 mg once weekly to placebo in patients treated with diet and exercise alone and found that both were superior to placebo at 52 weeks. The least squares mean difference from placebo in HbA1c was -0.84% with the 30 mg dose and -1.04% with the 50 mg dose (*Nauck et al 2016*).
  - HARMONY 3 demonstrated that albiglutide 30 mg to 50 mg once weekly was superior to placebo, sitagliptin 100 mg once daily, and glimepiride 2 to 4 mg daily in patients taking concurrent metformin at 2 years, with a mean reduction in HbA1c of 0.6% (*Ahren et al 2014*).
  - HARMONY 4 was an OL trial comparing albiglutide (30 mg to 50 mg once weekly) to protocol-titrated insulin glargine in patients taking concurrent metformin with or without an SFU. In this study, albiglutide demonstrated noninferiority to insulin glargine in HbA1c improvement at 52 weeks (*Weissman et al 2014*).
  - HARMONY 5 compared albiglutide (30 mg to 50 mg once weekly) to placebo and pioglitazone (30 mg to 45 mg per day) in patients taking concurrent metformin and glimepiride. At week 52, albiglutide did not meet the pre-specified noninferiority margin compared to pioglitazone; however, it was superior to placebo and had a mean reduction in HbA1c of 0.6% (*Home et al 2015*).
  - HARMONY 6, another OL trial, demonstrated that albiglutide 30 mg to 50 mg once weekly was noninferior to insulin lispro 3 times daily in patients taking concurrent pioglitazone with or without metformin at 26 weeks, with a mean reduction in HbA1c of 0.8% (*Rosenstock et al 2014a*).
  - HARMONY 7 was an OL study comparing albiglutide 50 mg once weekly to liraglutide 1.8 mg daily in patients taking concomitant metformin, TZD, SFU, or a combination of the medications. At week 32, the mean model adjusted change in HbA1c was -0.78% with albiglutide and -0.99% with liraglutide. Albiglutide failed to meet noninferiority ($p = 0.085$) (*Pratley et al 2014*).
  - HARMONY 8 demonstrated that albiglutide 30 mg to 50 mg was superior to sitagliptin 25 to 100 mg in patients with impaired renal function on concurrent agents or lifestyle treatment at 26 weeks, with a mean reduction in HbA1c of 0.8% compared to a reduction of 0.5% with sitagliptin (*Leiter et al 2014*).

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
  - AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (*Wysham et al 2014*).
  - AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (*Giorgino et al 2015*).
  - AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (*Umpierrez et al 2014*).
  - AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($p = 0.005$ and $p = 0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (*Blonde et al 2015*).
  - AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($p < 0.001$ for all comparisons) (*Nauck et al 2014, Weinstock et al 2015*).

- AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (*Dungan et al 2014*).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 PC, 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($p < 0.001$, $p < 0.002$, and $p < 0.0001$, respectively) (*Buse et al 2004, DeFronzo et al 2005, Kendall et al 2005*). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (*Blonde et al 2006, Buse et al 2007, Klonoff et al 2008, Ratner et al 2006, Riddle et al 2006*).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($p < 0.001$), fasting plasma glucose (FPG) ($p < 0.001$), and body weight ($p < 0.001$) compared to placebo (*Zinman et al 2007*).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($p < 0.001$ for both), whereas the SFU caused significant increases in both ($p < 0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $p < 0.001$ for all; glyburide; $p < 0.001$ for all). Only exenatide significantly improved insulin resistance ($p < 0.01$) and β-cell function ($p < 0.05$) (*Derosa et al 2010*).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $p = 0.002$) (*Gallwitz et al 2012*).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (*Bunck et al 2009, Bunck et al 2010, Davies et al 2009, Heine et al 2005, Nauck et al 2007, Secnik et al 2006*). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was "superior" in decreasing FPG (p value not reported and $p < 0.0001$), while in another trial there was no difference between the 2 treatments ($p = 0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (*Bunck et al 2009, Heine et al 2005, Nauck et al 2007*). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($p = 0.93$ for both) (*Secnik et al 2006*).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).
  - As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs. 35.0%) and vomiting (4.7% vs. 8.9%), and higher incidences of diarrhea (9.3% vs. 4.1%) and injection site-related AEs (13% vs. 10%) (*Blevins et al 2011*).
  - In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).

- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
  - In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
  - LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).

Lixisenatide

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
  - GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($p < 0.0001$) (*Fonseca et al 2012*).
  - GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs. placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs. -0.72% for the lixisenatide group. The difference vs. placebo was -0.46% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Bolli et al 2014*).
  - GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (*Yu et al 2014*).
  - GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2014b*).

- GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Pinget al 2013*).
- In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs. placebo (*Riddle et al 2013a*).
- In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (*Riddle et al 2013b, Seino et al 2012*).
- GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs. insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2016*).
- GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs. exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs. exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs. exenatide was 0.17% ($p = 0.0175$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2013*).
- A meta-analysis of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials for albiglutide (results expected in 2018) and dulaglutide (REWIND, results expected in 2018) (*ClinicalTrials.gov 2017)*. The EXSCEL trial examining exenatide ER was completed in 2017; the manufacturer announced that the drug met its primary objective of non-inferiority vs. placebo for the major adverse CV events (MACE) endpoint. The results of the EXSCEL trial will be presented at the European Association for the Study of Diabetes (EASD) annual meeting in September 2017 (*Astra Zeneca Press Release 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs. the placebo group (14.9%) (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs. the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; $p = 0.007$). The rate of death from any cause was lower in the liraglutide group (8.2%) vs. the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; $p = 0.02$). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
  - In June 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the FDA completed its meeting regarding the sponsor's supplemental New Drug Application (sNDA) for inclusion of the LEADER trial data in the label for liraglutide. The Advisory Committee voted 19-0 in favor of liraglutide on the question: "Do the results of LEADER trial establish that the use of liraglutide in patients with T2DM is not associated with excess CV risk?" It voted 17-2 in favor of liraglutide on the question: "Does the LEADER trial provide substantial evidence needed to establish that liraglutide (1.8 mg) reduces CV risk in patients with T2DM?" Regulatory feedback is expected in Q3 2017 (*Novo Nordisk Press Release 2017*).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs. placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo ($p < 0.001$), but did not demonstrate superiority ($p = 0.81$).

The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).

- Semaglutide, a once-weekly GLP-1 receptor agonist in the pipeline, demonstrated reduced CV risks in the SUSTAIN-6 trial when compared to placebo. A larger confirmatory trial is planned by Novo Nordisk, which is also expected to gather additional data on retinopathy complications reported in earlier studies (*Marso et al 2016b, Skydsgaard 2016*).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis (*Monami et al 2017a*) and appear to reduce all-cause mortality, CV mortality, and the incidence of MI (*Monami et al 2017b*) compared to placebo or other antidiabetic agents.

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; p = 0.0071) and was also associated with a significant weight loss compared to placebo (p < 0.001) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs. -0.18%; p = 0.012) and pramlintide 60 mcg 4 times daily (-0.39 vs -0.18%; p = 0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (p = 0.011 and p = 0.001 for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).
- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines state that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2017; Garber et al 2017, Inzucchi et al 2015*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).
- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, renal impairment, and lack of conclusive evidence for macrovascular risk reduction. Common AEs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea
- Albiglutide, exenatide, exenatide ER, liraglutide, and pramlintide are Pregnancy Category C. Dulaglutide and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.
  - Due to the long washout period for albiglutide, discontinuation of the drug at least 1 month before a planned pregnancy should be considered.
- Albiglutide, dulaglutide, and liraglutide have a Risk Evaluation and Mitigation Strategy (REMS) program consisting of a communication plan to inform healthcare providers about the potential risk of MTC and acute pancreatitis (*REMS@FDA Web site 2017*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tanzeum (albiglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Wait 15 minutes for the 30-mg pen and 30 minutes for the 50-mg pen after the lyophilized powder and diluent are mixed to ensure reconstitution.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, albiglutide, dulaglutide, liraglutide, and lixisenatide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, albiglutide, and dulaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial demonstrated reduced CV risk with liraglutide vs. placebo (*Marso et al 2016a*), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs. placebo (*Pfeffer et al 2015*). Results of the SUSTAIN-6 trial for semaglutide, an agent which has not yet been FDA approved, have also been published (*Marso et al 2016b*).
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Albiglutide, dulaglutide, and liraglutide have REMS programs which include a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines recommend that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. For T1DM, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (*ADA 2017; Garber et al 2017, Inzucchi et al 2015*).

REFERENCES

- Adlyxin [package insert], Bridgewater, NJ: Sanofi-Aventis; July 2016.
- Ahren B, Johnson SL, Stewart M, et al. Harmony 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014;37:2141-2148.
- American Diabetes Association. Diabetes basics. ADA Web Site. http://www.diabetes.org/diabetes-basics. Updated April 5, 2017. Accessed June 14, 2017.
- American Diabetes Association. Standards of medical care in diabetes (2017). *Diabetes Care*. 2017;40(suppl 1):S1-S135.
- AstraZeneca Press Release: Bydureon EXSCEL trial meets primary safety endpoint objective in type-2 diabetes patients at wide range of cardiovascular risk. May 23, 2017. https://www.astrazeneca.com/media-centre/press-releases/2017/bydureon-exscel-trial-meets-primary-safety-objective-in-type-2-diabetes-patients-at-wide-range-of-cardiovascular-risk-23052017.html. Accessed June 14, 2017.
- Bergenstal RM, Li Y, Porter TKB, et al. Exenatide once weekly improved glycaemic control, cardiometabolic risk factors and a composite index of an HbA1c < 7%, without weight gain or hypoglycaemia, over 52 weeks. *Diabetes Obes Metab*. 2013;15(3): 264-271.
- Bergenstal RM, Wysham C, MacConell L, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. *Lancet*. 2010;376:431-439.
- Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared to exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301-1310.
- Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet*. 2015;385(9982):2057-2066.
- Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight, and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab*. 2006;8(4):436-447.
- Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). *Diabet Med*. 2014;31(2):176-184.
- Broglio F, Mannucci E, Napoli R, et al. Beneficial effect of lixisenatide after 76 weeks of treatment in patients with type 2 diabetes mellitus: A meta-analysis from the GetGoal programme. *Diabetes Obes Metab*. 2017;19(2):248-256.
- Bunck MC, Corner A, Eliasson B, et al. One-year treatment with exenatide vs insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress. *Atherosclerosis*. 2010;212(1):223-229.
- Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves β-cell function, compared to insulin glargine, in metformin-treated type 2 diabetic patients. *Diabetes Care*. 2009;32:762-768.
- Buse JB, Henry RR, Han J, et al. Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27(11):2628-2635.
- Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of 2 years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of 3 double-blind, placebo-controlled trials. *Clin Ther*. 2007;29(1):139-153.
- Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomized, open-label study. *Lancet*. 2013;381(9861):117-124.
- Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day vs exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39-47.
- Buse JB, Sesti G, Schmidt WE, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care*. 2010;33:1,300-303.
- Bydureon [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals; March 2017.
- Byetta [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals; February 2015.
- Clinicaltrials.gov Web site. http://www.clinicaltrials.gov. Accessed June 14, 2017.
- Davies MJ, Donnelly R, Barnett AH, et al. Exenatide compared to long-acting insulin to achieve glycemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared to Long-Acting insulin (HEELA) study. *Diabetes Obes Metab*. 2009;11(12):1153-1162.
- DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28(5):1092-1100.
- Derosa G, Maffioli P, Salvadeo SAT, et al. Exenatide vs glibenclamide in patients with diabetes. *Diabetes Technol Ther*. 2010;12(3):233-240.
- Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomized trial. *Lancet*. 2010;375:2234-2243.
- Drucker D, Buse JB, Taylor K, et al. Exenatide once weekly vs twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
- DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed June 14, 2017.
- Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide in metformin-treated patients with Type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349-1357.
- FDA Drug Approval Package for Tanzeum (albiglutide) injection. Approval Letter. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125431Orig1s000TOC.cfm. Accessed June 14, 2017.
- Fonseca VA, Alvarado-Ruiz R, Raccah D, et al; for the EFC6018 GetGoal-Mono Study Investigators. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). *Diabetes Care*. 2012;35(6):1225-1231.
- Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label randomized controlled trial. *Lance*t.2012; 379:2270-2278.
- Garber A, Henry R, Ratner R, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-481.

- Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycemic control and weight for 2 years as monotherapy compared to glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13(4):348-356.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive diabetes management algorithm – 2017 executive summary. *Endocr Pract*. 2017. Available at: https://www.aace.com/publications/algorithm. Accessed June 14, 2017.
- Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38(12):2241-2249.
- Heine RJ, Van Gaal LF, Johns D, et al; GWAA Study Group. Exenatide vs insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143(8):559-569.
- Home P, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide vs placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes Obes Metab*. 2015;17:179-187.
- Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and Safety of Glucagon-like peptide-1 receptor agonists in type 2 diabetes: Systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19(4):524-536.
- Inagaki N, Atsumi Y, Oura T, et al. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. 2012;34(9):1892-1908.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2015;38(1):140-149.
- Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28(5):1083-1091.
- Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24(1):275-286.
- Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. *Diabetes Care*. 2014;37:2723-2730.
- Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26:268-278.
- Marso SP, Bain SC, Consoli A, et al; for the SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016b;375(19):1834-1844.
- Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016a;375(4):311-322.
- Monami M, Nreu B, Scatena A, et al. Safety issues with Glucagon-Like peptide-1 receptor agonists: Pancreatitis, pancreatic cancer, and cholelithiasis. data from randomised controlled trials. *Diabetes Obes Metab*. 2017a Feb 28. doi: 10.1111/dom.12926.
- Monami M, Zannoni S, Pala L, et al. Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials. *Int J Cardiol*. 2017b;240:414-421.
- Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. *Diabetes Care*. 2009;32:84-90.
- Nauck M, Frid A, Hermansen K, et al. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes Obes and Metab*. 2013;15(3):204–212.
- Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in Type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158.
- Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50(2):259-267.
- Nauck MA, Stewart MW, Perkins C, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetologia*. 2016;59(2):266-274.
- Novo Nordisk Press Release: Novo Nordisk receives positive 17-2 vote from FDA Advisory Committee that Victoza provides substantial evidence of cardiovascular risk reduction in patients with type 2 diabetes. June 20, 2017. http://www.novonordisk.com/bin/getPDF.2114627.pdf. Accessed June 20, 2017.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 7, 2017.
- Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257.
- Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). *Diabetes Obes Metab*. 2013;15(11):1000-1007.
- Pratley RE, Nauck MA, Barnett AH, et al; the HARMONY 7 Study Group. Once-weekly albiglutide, a GLP-1 receptor agonist, vs once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral agents. *Lancet Diabetes Endocrinol*. 2014;2(4):289-297.
- Qiao YC, Ling W, Pan YH, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Oncotarget*. 2017 Mar 8. doi: 10.18632/oncotarget.16008.
- Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med*. 2004;21(11):1204-1212.
- Ratner RE, Maggs D, Nielson LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2006;8(4):419-428.
- REMS@FDA Web site. 2017. http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed June 14, 2017.

- Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 1):52-week primary endpoint results from a randomized, double-blind, placebo-controlled, trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. *Diabetes Obes Metab*. 2014;16(12):1257-1264.
- Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care*. 2013b;36(9):2489-2496.
- Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes Care*. 2013a;36(9):2497-2503.
- Riddle MC, Henry RR, Poon TH, et al. Exenatide elicits sustained glycemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulfonylureas with or without metformin. *Diabetes Metab Res Rev*. 2006;22:483-491.
- Rosenstock J, Fonsecca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care*. 2014a; 37:2317-2325.
- Rosenstock J, Guerci B, Hanefeld M, et al.; GetGoal Duo-2 Trial Investigators. Prandial options to advance basal Insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 trial. *Diabetes Care*. 2016;39(8):1318-1328.
- Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). *J Diabetes Complications*. 2014b;28(3):386-392.
- Rosenstock J, Raccah D, Korányi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care*. 2013;36(10):2945-2951.
- Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4). *Diabetes Care*. 2012;35:252-258.
- Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. *Diabetologia*. 2009;52:2046-2055.
- Secnik Boye K, Matza LS, Oglesby A, et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. *Health Qual Life Outcomes*. 2006;4:80.
- Seino Y, Min KW, Niemoeller E, Takami A; EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab*. 2012;14(10):910-917.
- Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
- Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2011;13(2):169-180.
- Skydsgaard N. Novo plans larger study after encouraging semaglutide results. Reuters. http://www.reuters.com/article/us-health-diabetes-novo-nordisk-idUSKCN11M0F6. September 16, 2016. Accessed June 14, 2017.
- Sun F, Chai S, Li L, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. *J Diabetes Res*. 2015;2015:157201.
- Symlin [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals; April 2016.
- Tanzeum [package insert], Wilmington, DE: GlaxoSmithKline LLC; September 2016.
- Trulicity [package insert], Indianapolis, IN: Eli Lilly and Company; February 2017.
- Umpierrez G, Povedano ST, Manghi FP, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37:2168-2176.
- Victoza [package insert], Princeton, NJ: Novo Nordisk Inc.; April 2016.
- Wang B, Zhong J, Lin H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obes Metab*. 2013;15(8):737-749.
- Weinstock RS, Guerci B, Umpierrez G, et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. *Diabetes Obes Metab*. 2015;17:849-858.
- Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomized clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. 2014;57:2475-2484.
- Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care*. 2002;25(4):724-730.
- Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in Type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37:2159-2167.
- Yu Pan C, Han P, Liu X, et al. Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia). *Diabetes Metab Res Rev*. 2014;30(8):726-735.
- Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32(7):1224-1230.
- Zinman B, Hoogwerf BJ, Duran Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes. *Ann Intern Med*. 2007;146:477-485.

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Therapeutic Class Overview
Insulin and Incretin Mimetic combination agents

INTRODUCTION

- Diabetes is a tremendous burden on the United States (US) healthcare system. In 2013, diabetes was the 7th leading cause of death in the US. More than 29 million people, or 9.3% of the US population, are estimated to have diagnosed or undiagnosed diabetes (Centers for Disease Control [CDC], 2014).
- The classification of diabetes includes four clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (American Diabetes Association [ADA], 2017).
- The gold standard measure to assess average glycemic exposure in the diagnosis and treatment of T2DM is glycated hemoglobin (HbA1c). HbA1c reflects the average blood glucose (BG) levels over the past 12 weeks including both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). The exact contributions of PPG and FPG increments to the measure of hyperglycemia and its role in the development of both micro- and macrovascular complications of diabetes remain controversial (Monnier et al, 2011; Monnier et al, 2003).
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides (GLNs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, insulin, and glucagon-like peptide-1 (GLP-1) receptor analogs, also referred to as incretin mimetics.
  - Insulin is used as replacement therapy, and there are three basal insulin agents that are Food and Drug Administration (FDA)-approved (insulin detemir [LEVEMIR®], insulin degludec [TRESIBA®], insulin glargine [LANTUS® and TOUJEO®], and follow-on biologic insulin glargine [BASAGLAR®]). As a class of medications, the basal insulins are effective at lowering HbA1c and provide a nearly universal response. In the United Kingdom Prospective Diabetes Study (UKPDS), a reduced risk of microvascular events (eg, neuropathy, retinopathy, and nephropathy) was observed with use; however, insulin products are associated with hypoglycemia and weight gain (ADA, 2017; Prescribing information: BASAGLAR, 2016; LANTUS, 2016; LEVEMIR, 2015; TOUJEO, 2015; TRESIBA, 2015).
  - The GLP-1 receptor agonists (albiglutide [TANZEUM®], dulaglutide [TRULICITY®], exenatide [BYETTA®], exenatide ER [BYDUREON®], liraglutide [VICTOZA®], and lixisenatide [ADLYXIN™]) were developed to mimic the effects of endogenous GLP-1. Due to their extended half-lives, albiglutide, dulaglutide, and exenatide ER are dosed once weekly. Liraglutide and lixisenatide are dosed once daily, while exenatide is dosed twice daily. Of the GLP-1 receptor agonists, liraglutide is the only agent which has been shown to reduce CV and all-cause mortality when added to standard care. As a class of medications, the GLP-1 receptor agonists can cause hypoglycemia but not to the same degree as other oral anti-diabetic agents (OADs) and/or injectable agents. Additionally, they are known to decrease weight gain, increase gastrointestinal (GI)-related adverse events, and have been correlated with pancreatitis and c-cell hyperplasia/medullary thyroid tumors (ADA, 2017; Prescribing information: ADLYXIN, 2016; BYDUREON, 2015; BYETTA, 2015; TANZEUM, 2016; TRULICITY, 2017; VICTOZA, 2016).
- This review will focus on the long-acting insulin and GLP-1 receptor agonist combination products outlined in Table 1 for their respective FDA-approved indications.
- Medispan class: Insulin – Incretin Mimetic Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SOLIQUA™ 100/33 (insulin glargine/lixisenatide)	Sanofi-Aventis	11/21/2016	-
XULTOPHY® 100/3.6 (insulin degludec/liraglutide)	Novo Nordisk	11/21/2016	-

(DRUGS@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	SOLIQUA (insulin glargine/ lixisenatide)	XULTOPHY (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on:		
Basal insulin (<60 U daily) or lixisenatide	✔	--
Basal insulin (<50 U daily) or liraglutide (≤1.8 mg daily)	--	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	✔
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(Prescribing information: SOLIQUA, 2016; XULTOPHY, 2016)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Overview

- XULTOPHY, a combination of insulin degludec 100 U/mL and liraglutide 3.6 mg/mL, and SOLIQUA, a combination of insulin glargine 100 U/mL and lixisenatide 33 mcg/mL, have been approved for use in patients with T2DM who are inadequately controlled on basal insulin, or a GLP-1 receptor agonist (specifically liraglutide or lixisenatide, respectively). Insulin degludec/liraglutide reduced HbA1c more than its individual components when added to either metformin, pioglitazone, or a SFU. When added to metformin, insulin glargine/lixisenatide reduced HbA1c significantly more than insulin glargine alone. Insulin glargine/lixisenatide and insulin degludec/liraglutide are not FDA-approved for use in patients previously uncontrolled on OADs; therefore, these trials have been excluded from this review unless addressing comparative data in a class not addressed elsewhere.

SOLIQUA (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in two Phase 3, active-comparator (AC), open-label (OL), randomized controlled trials (RCTs), titled the LIXILAN trials:
  - o T2DM patients uncontrolled on basal insulin: The LIXILAN-L trial was a two-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least six months at stable daily doses of 15 to 40 U ± OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (N=366) or insulin glargine 100 U/mL (N=365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the least square mean difference (LSMD) between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, −0.5%; 95% confidence interval [CI], −0.6 to −0.4; P<0.0001) (Aroda et al, 2016; FDA briefing document [SOLIQUA], 2016; FDA summary review [SOLIQUA], 2016).
  - o Comparative data vs. GLP-1 receptor agonists: The LIXILAN-O trial was a three-treatment arm study in 1,167 patients with T2DM who were inadequately controlled on metformin ± OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (N=468), insulin glargine 100

U/mL (N=466), or lixisenatide (N=233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). Both co-primary hypotheses were required to be established before the step-down testing procedure for the secondary efficacy endpoints, which included a test of superiority of insulin glargine/lixisenatide over insulin glargine. After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, −0.3%; 95% CI, −0.4 to −0.2; P<0.0001) and also demonstrated superiority for the endpoint (P<0.0001). At week 30, the LSMD between insulin glargine/lixisenatide and lixisenatide was also statistically different for the primary endpoint (LSMD, −0.8%; 95% CI, −0.9 to −0.7; P<0.0001) (Rosenstock et al, 2016; FDA briefing document [SOLIQUA], 2016; FDA summary review [SOLIQUA], 2016).

- o Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin glargine/lixisenatide and insulin glargine; however, a fewer proportion of lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs. 25.6%, respectively) (Aroda et al, 2016**;** Rosenstock, et al, 2016; FDA summary review [SOLIQUA], 2016).

XULTOPHY (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in nine Phase 3, parallel-group, AC, RCTs, titled the DUAL trials (XULTOPHY dossier, 2016). Currently, results from DUAL I through V are available, and DUAL VII through IX are on-going; therefore, results are not available. The DUAL I and IV trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - o T2DM patients uncontrolled on basal insulin and OADs:
    - The DUAL II trial was a two-treatment arm, double-blinded (DB) study in 413 T2DM patients which compared insulin degludec/liraglutide (N=207) to insulin degludec (N=206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The estimated treatment difference (ETD) for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; P<0.0001) (Buse et al, 2014).
    - The DUAL V trial was a two-treatment arm, OL, non-inferiority study in 557 T2DM patients which compared insulin degludec/liraglutide (N=278) to insulin glargine (N=279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI <0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; P<0.001 for non-inferiority) (Lingvay et al, 2016).
  - o T2DM patients uncontrolled on GLP-1 receptor agonists: The DUAL III trial was a two-treatment arm, OL study in 438 T2DM patients which compared insulin degludec/liraglutide (N=292) to the currently administered maximum dose of GLP-1 receptor agonist (N=146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. Internationally-approved doses of GLP-1 receptor agonists do not match FDA-approved doses. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; P<0.001) (Linjawi et al, 2017).
  - o Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; P<0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs. the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine, demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; P<0.001) (Buse et al, 2014; Lingvay et al, 2016; Linjawi et al, 2017; XULTOPHY dossier, 2016).

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous myocardial infarction (MI), stroke, angina, or coronary, carotid, or peripheral arterial revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary endpoints of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (hazard ratio [HR], 1.02; 95% CI, 0.94 to 1.11; P=0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; P=0.27) (Gerstein et al, 2012).
  - A multi-center (MC), DB, randomized, placebo-controlled (PC) trial (ELIXA trial; N=6,068) was conducted to evaluate the long-term effects of lixisenatide vs. placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (P<0.001), but did not demonstrate superiority (P=0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (Pfeffer et al, 2015).
  - A MC, DB, randomized, PC trial (LEADER trial; N=9,340) was conducted to evaluate the long-term effects of liraglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide group (13%) vs. the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs. the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs. the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; P=0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (Marso et al, 2016).
  - In 2015, insulin degludec was FDA-approved based on interim data from the DEVOTE trial which assessed CV risk; however, the full results of the DEVOTE trial are anticipated to be available in 2017 (Novo Nordisk press release [DEVOTE], 2016).
- According to reputable guidelines, the combination of both a GLP-1 receptor agonist and a basal insulin is generally reserved for third- or fourth-line treatment in patients who are inadequately controlled after a trial and failure of other agents. Combination insulin therapy may be initiated in patients with an HbA1c ≥10%, BG ≥300 mg/dL, or in patients who are markedly symptomatic; if HbA1c is not controlled, then combination injectable therapy may be considered (ADA, 2017; Garber et al, 2017).

SAFETY SUMMARY

- Contraindications:
  - All agents in class are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
  - XULTOPHY (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Boxed warnings:
  - Due to the liraglutide component of XULTOPHY, there is a boxed warning and a warning and precaution associated with thyroid C-cell tumors in rats and mice. It is unknown if they cause thyroid C-cell tumors including MTC in humans.
- Warnings/Precautions:
  - Warnings and precautions for the class are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, the potential for fluid retention and HF with use of TZDs, and

the lack of clinical studies showing macrovascular risk reductions. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
  - Additional warnings and precautions for SOLIQUA include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control.
- Adverse events:
  - The most common adverse reactions reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common adverse reactions include hypoglycemia and allergic reactions with SOLIQUA and increased lipase reports with XULTOPHY.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- Risk Evaluation and Mitigation Strategy (REMS) programs:
  - As with other liraglutide-containing products, there is a REMS program for XULTOPHY, which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of MTC (REMS@FDA, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
SOLIQUA (insulin glargine/ lixisenatide)	Prefilled pen (100 U and 33 mcg/mL): 3 mL prefilled pen in packages of 5 pens, with each pen delivering 46 possible dosages ranging from 15 U/5 mcg to 60 U/20 mcg	Initial (*previously treated with lixisenatide or <30 U of basal insulin*): 15 U (15 U of insulin glargine and 5 mcg of lixisenatide) SC once daily; Initial (*previously treated with 30 to 60 U of basal insulin*): 30 U (30 U of insulin glargine and 10 mcg of lixisenatide) SC once daily; Maximum: 60 U (60 U of insulin glargine and 20 mcg of lixisenatide) SC once daily	Titrate or taper doses by 2 to 4 U every week based on metabolic needs, BG monitoring, and glycemic control. For patients who require daily doses below 15 U or over 60 U, an alternative antidiabetic agent should be prescribed.	Discontinue GLP-1 receptor agonist or a basal insulin prior to therapy initiation. Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day. After first use, pens should be discarded after 14 days.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
XULTOPHY (insulin degludec/ liraglutide)	Prefilled pen (100 U and 3.6 mg/mL): 3 mL prefilled pen in packages of 5 pens, with each pen delivering 41 possible dosages ranging from 10 U/0.36 mg to 50 U/1.8 mg	Initial: 16 U (16 U of insulin glargine and 0.58 mg of liraglutide) SC once daily; Maximum: 50 U (50 U of insulin glargine and 1.8 mg of liraglutide) SC once daily	Titrate or taper doses by 2 U every 3 to 4 days based on metabolic needs, BG monitoring, and glycemic control. The dosage may be temporarily down titrated to below 16 U (ie, 10 to 15 U); however, an alternative therapy should be used if patients require persistent dosages below 16 U. For patients who require daily doses below 16 U or over 50 U, an alternative antidiabetic agent should be prescribed.	Discontinue GLP-1 receptor agonist or a basal insulin prior to therapy initiation. Inject in the abdomen, thigh, or upper arm. Administer at the same time every day with or without food. After first use, pens should be discarded after 21 days.

Abbreviations: BG = blood glucose; GLP-1 = glucagon-like peptide; SC = subcutaneously; U = unit

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
SOLIQUA* (insulin glargine/ lixisenatide)	Of the patients treated with SOLIQUA, a total of 25.2% were ≥65 years of age, and 4% were ≥75 years of age. No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out. Hypoglycemia	Safety and efficacy have not been established.	The effect of renal impairment on SOLIQUA has not been studied. *Insulin glargine*: Increased levels of insulin have been observed in renal failure. *Lixisenatide*: Mild and moderate renal impairment require no dose adjustment. Only five patients with severe impairment have been exposed; therefore,	The effect of hepatic impairment on SOLIQUA has not been studied; however, monitoring should be intensified.	Category C† was assigned to insulin glargine mono-therapy previously. No well-controlled studies with SOLIQUA have been conducted in pregnancy; use only if the potential benefit outweighs the risk. Endogen-ous insulin is present in human milk. Lixisenatide is present in the milk of animal models.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	may be difficult to detect in the elderly.		use should be closely monitored for GI AE and changes in renal function. SOLIQUA is not recommended in ESRD.		An assessment of the risks and benefits should be considered prior to nursing.
XULTOPHY* (insulin degludec/ liraglutide)	Of the patients treated with XULTOPHY, a total of 19.9% were ≥65 years of age, and 2.8% were ≥75 years of age. No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out. Hypoglycemia may be difficult to detect in the elderly.	Safety and efficacy have not been established.	There is limited mild to moderate renal impairment experience with XULTOPHY, and no severe impairment experience. *Insulin degludec*: There are no clinically relevant PK differences in renal impairment. *Liraglutide*: This drug was evaluated in a 26-week study of moderate renal impairment patients. There is limited experience in severe impairment or ESRD. Post-marketing reports of acute or worsening chronic renal failure have been reported.	The effect of hepatic impairment on XULTOPHY has not been studied. *Insulin degludec*: There are no clinically relevant PK differences in hepatic impairment. *Liraglutide*: There is limited experience in patients with mild to severe hepatic impairment.	No well-controlled studies with XULTOPHY have been conducted in pregnancy; use only if the potential benefit outweighs the risk. Insulin degludec and liraglutide are present in the milk of animal models. An assessment of the risks and benefits should be considered prior to nursing.

Abbreviations: AE = adverse event; ESRD = end stage renal disease; GI = gastrointestinal; PK = pharmacokinetic
*Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.
†Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Insulin glargine/lixisenatide (SOLIQUA) and insulin degludec/liraglutide (XULTOPHY) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult T2DM patients who are uncontrolled on a basal insulin or lixisenatide and liraglutide, respectively. The indication for both agents has dose limitations: XULTOPHY is indicated for patients uncontrolled on <50 U daily of a basal insulin or ≤1.8 mg daily of liraglutide, and SOLIQUA is indicated for patients uncontrolled on <60 U daily of a basal insulin. Neither agent is FDA-approved for use in T2DM patients who are uncontrolled on OADs.
- The medications are administered through a fixed ratio pen. SOLIQUA may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while XULTOPHY may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages.

Individualized dosing is recommended based on metabolic needs, BG monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.

- The insulin and incretin mimetic combination agents have been studied in combination with metformin, SFU, pioglitazone, and GLN. In studies, SOLIQUA demonstrated HbA1c reductions ranging from 0.3 to 0.5% versus insulin glargine and 0.8% versus lixisenatide. XULTOPHY demonstrated estimated treatment differences in HbA1c reductions of 1% versus insulin degludec monotherapy, 0.6% versus insulin glargine monotherapy, and 0.9% versus a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, XULTOPHY and SOLIQUA were associated with both weight losses and gains. Hypoglycemia rates are mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with less hypoglycemic events (Aroda et al, 2016**;** FDA summary review [SOLIQUA], 2016; Buse et al, 2014; Lingvay et al, 2016; Linjawi et al, 2017; Rosenstock, et al 2016). Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo (Gerstein et al, 2012; Marso et al, 2016; Pfeffer et al, 2015).
- Overall, the safety profiles of the insulin and incretin mimetic combination agents are similar. A few differences are that XULTOPHY has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. There is also a REMS program for XULTOPHY which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC. Other key warnings for these drugs include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and HF with use of TZDs. SOLIQUA has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common adverse reactions include GI effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. Combination injection therapy (including the combination of a GLP-1 receptor agonist and a basal insulin) is generally reserved for third- or fourth-line treatment in patients who are inadequately controlled after a trial and failure of other agents. Combination injection therapy may be initiated in severely uncontrolled T2DM patients who present with an HbA1c ≥10%, BG ≥300 mg/dL, or in those who are markedly symptomatic at baseline (ADA 2017; Garber et al, 2017; Inzucchi et al, 2015).

REFERENCES

- ADLYXIN prescribing information. Sanofi-Aventis. Bridgewater, NJ. July 2016.
- American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017;40(suppl 1):S1-S135.
- Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. Diabetes Care. 2016;39(11):1972-1980.
- BASAGLAR prescribing information. Lilly USA, LLC. Indianapolis, IN. June 2016.
- Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ration combination of insulin degludec and liraglutide (IDegLira). Diabetes Care. 2014; 37(11):2926-33.
- BYDUREON prescribing information. AstraZeneca Pharmaceuticals. Wilmington, DE. September 2015.
- BYETTA prescribing information. AstraZeneca Pharmaceuticals. Wilmington, DE. February 2015.
- Centers for Disease Control and Prevention (CDC). Diabetes Report Card 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2015. Available at: http://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2014.pdf. Accessed January 3, 2016.
- Drugs@FDA.com: Approved Drug Products with Therapeutic Equivalence Evaluations. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed January 19, 2017.
- FDA briefing document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting - Soliqua/insulin glargine and lixisenatide. Food and Drug Administration Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM502558.pdf. Accessed January 9, 2016.
- FDA summary review: Soliqua/insulin glargine and lixisenatide. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208673Orig1s000SumR.pdf. Accessed January 9, 2016.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive diabetes management algorithm – 2017 executive summary. Endocr Pract. 2017. Available at: https://www.aace.com/publications/algorithm. Accessed January 24, 2017.
- Gerstein HC, Bosch J, Dagenais GR, et al; for the ORIGIN trial investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319-28.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015;38(1):140-149.
- LANTUS prescribing information. Sanofi US. Bridgewater, NJ. July 2015.
- LEVEMIR prescribing information. Novo Nordisk Inc. Plainsboro, NJ. February 2015.

- Lingvay I, Perez MF, Garcia-Hernandez P, et al. Effect of Insulin Glargine Up titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial. JAMA. 2016;315(9):898-907.
- Linjawi S, Bode BW, Chaykin LB, et al. The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial. Diabetes Ther. 2017;8(1):101-14.
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER trial). N Engl J Med. 2016;375(4):311-322.
- Monnier L, Colette C, Owens D et al. Postprandial and basal glucose in type 2 diabetes: assessment and respective impacts. Diabetes Care. 2011;13(Suppl 1):S25-32.
- Monnier L, Lapinski H, Colette C, et al. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care. 2003;26(3):881-5.
- Novo Nordisk press release (DEVOTE). Tresiba demonstrates a safe cardiovascular profile and reduces the risk of severe hypoglycaemia compared to insulin glargine U100 in the DEVOTE trial. Available at: https://globenewswire.com/news-release/2016/11/29/893585/0/en/Novo-Nordisk-A-S-Tresiba-demonstrates-a-safe-cardiovascular-profile-and-reduces-the-risk-of-severe-hypoglycaemia-compared-to-insulin-glargine-U100-in-the-DEVOTE-trial.html. Accessed March 7, 2017.
- Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247-2257.
- REMS@FDA: Approved Risk Evaluation and Mitigation Strategies (REMS). Available at: http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed March 13, 2017.
- Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. Diabetes Care. 2016;39(11):2026-2035.
- SOLIQUA prescribing information. Bridgewater, NJ: Lilly Sanofi-Aventis US, LLC; November 2016.
- TANZEUM prescribing information. GlaxoSmithKline LLC. Wilmington, DE. September 2016.
- TRULICITY prescribing information. Eli Lilly and Company. Indianapolis, IN. January 2017.
- TOUJEO prescribing information. Sanofi US. Bridgewater, NJ. May 2015.
- TRESIBA prescribing information. Novo Nordisk Inc. Plainsboro, NJ. September 2015.
- VICTOZA prescribing information. Novo Nordisk Inc. Princeton, NJ. April 2016.
- XULTOPHY dossier. Novo Nordisk Inc. Plainsboro, NJ. 2016.
- XULTOPHY prescribing information. Novo Nordisk Inc. Plainsboro, NJ. November 2016.

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Therapeutic Class Overview
Sodium-Glucose Cotransporter 2 Inhibitors

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States *(Centers for Disease Control and Prevention [CDC] 2017)*.
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2017[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2017[b])*.
- Complications of T2DM include hypertension, heart disease, stroke, vision loss, kidney disease, and neuropathy. It is the leading cause of kidney failure and the seventh leading cause of death in the U.S. *(National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 2017, CDC 2017)*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2017)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing rate of hepatic glucose production, decreasing rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2017, Inzucchi et al 2015)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The SGLT2 inhibitor class consists of three agents, canagliflozin, dapagliflozin, and empagliflozin, and their combination products.
- Medispan class: Sodium-glucose cotransporter 2 inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dapagliflozin products	
Farxiga (dapagliflozin)	-
Xigduo XR (dapagliflozin/metformin hydrochloride extended-release)	-
Qtern (dapagliflozin/saxagliptin)	-
Canagliflozin products	
Invokana (canagliflozin)	-
Invokamet (canagliflozin/metformin hydrochloride)	-
Invokamet XR (canagliflozin/metformin extended-release)	-
Empagliflozin products	
Jardiance (empagliflozin)	-
Glyxambi (empagliflozin/linagliptin)	-
Synjardy (empagliflozin/metformin)	-
Synjardy XR (empagliflozin/metformin extended-release)	-

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Single Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR† (canagliflozin/ metformin)	Synjardy, Synjardy XR† (empagliflozin/ metformin)	Xigduo XR† (dapagliflozin/ metformin ER)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓					
To reduce the risk of cardiovascular (CV) death in adult patients with T2DM and established CV disease			✓					
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin/dapagliflozin/empagliflozin and metformin is appropriate.						✓	✓*	✓
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate				✓*				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin					✓			

† These combination products contain metformin extended-release (ER).

* Products containing empagliflozin include the clinical trial information on EMPA-REG OUTCOME study as well as the following statement in the indications section: The effectiveness of Glyxambi/Synjardy/Synjardy XR on reducing the risk of CV death in adults with T2DM and CV disease has not been established.

Limitations of use: Canagliflozin, dapagliflozin, and empagliflozin are not recommended in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis (DKA). Glyxambi has not been studied in patients with a history of pancreatitis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

(*Prescribing information: Farxiga 2017, Glyxambi 2017, Invokana 2017, Invokamet 2017, Invokamet XR 2017, Jardiance 2016, Qtern 2017, Synjardy 2016, Synjardy XR 2016, Xigduo XR 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of the SGLT2 inhibitors were evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. SGLT2 inhibitors have demonstrated efficacy in lowering glycosylated hemoglobin (HbA1c) levels by ~0.5% to 1% *(Inzucchi et al 2015)*. They have been studied as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose (FPG), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
  - As monotherapy *(Bailey et al 2012, Ferrannini et al 2010, Ferrannini et al 2013, Inagaki et al 2014, Stenlöf et al 2013)*
  - With metformin *(Bailey et al 2010, Haring et al 2014, Henry et al 2012, Leiter et al 2015, Rosenstock et al 2013, Rosenstock et al 2016, Ross et al 2015)*
  - With an SFU *(Fulcher et al 2015, Strojek et al 2011, Strojek et al 2014, Wilding et al 2013)*
  - With metformin and an SFU *(Haring et al 2013, Matthaei et al 2015)*
  - As add-on therapy to TZDs *(Forst et al 2014, Kovacs et al 2014, Rosenstock et al 2012)*
  - As add-on therapy or compared to DPP-4 inhibitors *(Jabbour et al 2014, Lavalle-Gonzalez et al 2013, Roden et al 2013, Rosenstock et al 2015[a], Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015[b], Wilding et al 2012)*
- The combination of SGLT2 inhibitors with metformin lower HbA1c compared to placebo. These studies use the coadministration of the two components instead of fixed-dose combination tablets for Invokamet, Synjardy, and Xigduo XR. The bioequivalency of Invokamet XR and Synjardy XR to the immediate release combination products in healthy subjects was used to support the Food and Drug Administration (FDA) approval of these extended-release combination products.
- Glyxambi (empagliflozin/linagliptin) was the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized controlled trial (RCT) in patients with T2DM demonstrated reductions in HbA1c with Glyxambi that were superior to those of empagliflozin or linagliptin alone as add-on to metformin *(DeFronzo et al 2015)*. Qtern (dapagliflozin/saxagliptin) was approved in February 2017; efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015)* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs. the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[a])*.
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to SFUs:
  - Dapagliflozin vs. glipizide, both in combination with metformin *(Nauck et al 2011)*
  - Canagliflozin vs. glimepiride *(Cefalu et al 2013)*
  - Empagliflozin vs. glimepiride *(Ridderstrale et al 2014)*
- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
  - Patients with T2DM and chronic kidney disease *(Barnett et al 2014, Kohan et al 2014, Yale et al 2014, Yale et al 2013)*
  - Patients with T2DM and CV disease *(Leiter et al 2014)*
  - Elderly patients *(Bode et al 1995, Bode et al 2015, Sinclair et al 2014, Sinclair et al 2016)*
    - A pooled analysis of six phase 3, double-blind, placebo-controlled, RCTs compared the efficacy and safety of canagliflozin in patients < 75 years and ≥ 75 years of age. Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted mean reductions in HbA1c in patients < 75 years (-0.69% and -0.85%, respectively) and ≥ 75 years (-0.65% and -0.55%, respectively). Dose-related reductions in FPG, body weight, and blood pressure were also seen with canagliflozin 100 mg and 300 mg in patients in both age groups. Overall adverse event incidences were 67.1% with canagliflozin 100 mg, 68.6% with canagliflozin 300 mg, and 65.9% with non-canagliflozin (pooled group of comparators in all studies) in patients < 75 years, and 72.4%, 79.1%, and 72.3%, respectively, in patients ≥ 75 years, with a similar safety profile in both groups *(Sinclair et al 2016).*
- Various long-term studies have been conducted that provide data on the safety and efficacy after at least one year of treatment with the SGLT2 inhibitors *(Araki et al 2015, Bailey et al 2015, Bode et al 2015, Del Prato et al 2015, Kovacs et al 2015, Nauck et al 2014)*.
- Other post-hoc analyses of pooled data from RCTs have further evaluated the effects of SGLT2 inhibitors on parameters such as blood pressure, weight gain, and adverse events *(Davies et al 2015, Ptaszynska et al 2014, Weir et al 2014)*.

- Furthermore, various meta-analyses have been conducted that have demonstrated the individual efficacy of the SGLT2 inhibitors *(Liakos et al 2014, Orme et al 2014, Sun et al 2014, Yang et al 2014)*.

Comparative efficacy

- While there are no head-to-head studies comparing the efficacy and safety of the SGLT2 inhibitors, a 2016 systematic review and network meta-analysis found that canagliflozin 300 mg reduced HbA1c, FPG, and systolic blood pressure, while increasing low-density lipoprotein cholesterol (LDL-C) to a greater extent compared with other inhibitors (dapagliflozin and empagliflozin) at any dose *(Zaccardi et al 2016)*.
- Another systematic review and network meta-analysis found similar results *(Shyangdan et al 2016)*. When used as monotherapy, a greater proportion of patients achieved a HbA1c <7% on canagliflozin 300 mg than on canagliflozin 100 mg and dapagliflozin 10 mg, but there were no significant differences compared with either dose of empagliflozin. Canagliflozin 300 mg reduced HbA1c more than other SGLT-2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. There were no significant differences between the SGLT2 inhibitors with respect to weight reduction.
- The Agency for Healthcare Research and Quality (AHRQ) updated its review of the diabetes medications for adults with T2DM to include the results from an additional eight studies *(Bolen et al 2016)*. Findings related to the SGLT2 inhibitors included some of the following:
  - Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.
  - Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin.
  - Some adverse events were higher with specific classes of drugs including gastrointestinal (GI) events (metformin and GLP-1 agonists) and risk of genital mycotic infection (SGLT2 inhibitors).

Cardiovascular outcomes studies

- EMPA-REG OUTCOME was the first study to demonstrate a positive benefit on CV outcomes due to glucose lowering with empagliflozin as add-on to standard of care in T2DM patients with high CV risk *(Zinman et al 2015)*. Empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) by 14% vs. placebo ($p < 0.001$ for non-inferiority; $p = 0.04$ for superiority). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure (HHF), and 32% reduction in death from any cause associated with its use; however, there were no significant between-group differences in the rates of MI or stroke. The underlying mechanism of empagliflozin and its effect on CV outcomes are not clearly understood. Recently updated guidelines acknowledge the established CV benefit with empagliflozin *(ADA 2017, Garber et al 2017)*.
  - A recently published follow-up to the EMPA-REG OUTCOME study examined the pre-specified secondary objective of the effect of empagliflozin on microvascular outcomes, and in particular, progression of kidney disease in patients with T2DM at high risk for CV events. In this new analysis, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs. 18.8%; hazard ratio [HR]: 0.61; 95% confidence interval [CI], 0.53 to 0.70; $p < 0.001$). This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death. A relative risk reduction of 38% was seen with the endpoint of progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs.16.2%; HR: 0.62; 95% CI, 0.54 to 0.72; $p < 0.001$) *(Wanner et al 2016)*.
- The CANVAS Program was comprised of 2 trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), that included a total of 10,142 patients with T2DM and high CV risk *(Neal et al 2017)*. The studies were designed to assess the CV safety and efficacy of canagliflozin, as well as to evaluate the balance between potential benefits of the drug and its associated risks (eg, genitourinary infection, DKA, fracture). Significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- A Phase 3, multicenter trial to evaluate the effect of dapagliflozin on the incidence of CV events, known as DECLARE-TIMI58, is currently underway with results expected by 2019 *(ClinicalTrials.gov)*.
- The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD REAL) study is the first large real-world study of > 300,000 patients with T2DM, both with and without established cardiovascular disease (CVD) that evaluated outcomes of HHF and all-cause death in patients with T2DM treated with SGLT2 inhibitors vs. other glucose-lowering drugs. Data were collected from patients living in 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) *(Kosiborod et al 2017)*. Overall, treatment with SGLT2 inhibitors

vs. other agents was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

CLINICAL GUIDELINES

Overview

- Several consensus guidelines recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2017[b], Copeland et al 2013, Inzucchi et al 2015)*. Metformin is considered the drug of choice for children with T2DM *(Copeland et al 2013)*.

- ADA/European Association for the Study of Diabetes (EASD) - Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach *(Inzucchi et al 2015)*
  - Monotherapy: Metformin remains the optimal drug for monotherapy due to its low cost, proven safety record, weight neutrality, and possible benefits on CV outcomes.
    - In patients intolerant of, or with contraindications for, metformin, an initial drug from other classes discussed under "Dual therapy" should be considered.
  - Dual therapy: If the HbA1c target is not achieved after ~3 months with metformin monotherapy, adding one of the six treatment options below may be considered (listed order is not meant to denote any specific preference). Other drugs (eg, alpha-glucosidase inhibitors, colesevelam, bromocriptine, and pramlintide) may be tried in specific situations but are generally not favored due to modest efficacy, the frequency of administration, and/or side effects. For all patients, initiating therapy with a dual combination should be considered when HbA1c is ≥ 9% (75 mmol/mol) in order to achieve the HbA1c target more expeditiously.
    - SFU (rapid-acting secretagogues [meglitinides] may be used instead of SFUs in patients with irregular meal schedules or those who develop late postprandial hypoglycemia on an SFU).
    - TZD
    - DPP-4 inhibitor
    - SGLT2 inhibitor
    - GLP-1 receptor agonist
    - Basal insulin
  - Triple therapy: Triple therapy may be considered if the HbA1c goal is not achieved after 3 months with dual therapy. Options for triple therapy include (order is not meant to denote any specific preference):
    - Metformin + SFU + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + TZD + (SFU or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist or insulin)
    - Metformin + DPP-4 inhibitor + (SFU or TZD or SGLT2 inhibitor or insulin)
    - Metformin + SGLT2 inhibitor + (SFU or TZD or DPP-4 inhibitor or insulin)
    - Metformin + GLP-1 receptor agonist + (SFU or TZD or insulin)
    - Metformin + basal insulin + (TZD or DPP-4 inhibitor or SGLT2 inhibitor or GLP-1 receptor agonist)
  - Combination injectable therapy: If the HbA1c goal is not achieved after 3 months with triple therapy and the patient is (1) on oral combination, moving to injectables is recommended; (2) on GLP-1 receptor agonist therapy, adding basal insulin is recommended; (3) on optimally treated basal insulin, adding a GLP-1 receptor agonist or mealtime insulin is recommended. In refractory patients, adding a TZD or SGLT2 inhibitor may be considered.
    - Initial therapy at this stage should be considered when blood glucose is ≥ 300 to 350 mg/dL (≥ 16.7 to 19.4 mmol/L) and/or HbA1c ≥ 10 to 12% (≥ 86 to 108 mmol/mol), especially if the patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen.

- American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) -Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm *(Garber et al 2017)*
  - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication selection should consider antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other adverse events, tolerability, ease of use, likely adherence, cost,

and safety in heart, kidney, or liver disease. Minimizing the risks of hypoglycemia and weight gain are priorities. These guidelines recommend the following therapies:

- Lifestyle therapy, including a medically assisted weight loss program, is recommended for all patients.
- Should patients not achieve their goal HbA1c in three months, it is recommended that they escalate and add on therapy (medication options listed in order of recommended choice):

For HbA1c of < 7.5%:

- Monotherapy: Metformin, a GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, or an alpha-glucosidase inhibitor. TZD or SFU/glinide should be used with caution.

For HbA1c of ≥ 7.5%:

- Dual therapy: Metformin or another first-line agent + a second agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine quick release [QR], or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.
- Triple therapy: Metformin or another first-line agent + a second-line agent + a third agent (eg, GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, colesevelam, bromocriptine QR, or an alpha-glucosidase inhibitor). TZD, basal insulin, or SFU/glinide should be used with caution.
- If triple therapy fails to achieve the HbA1c goal in three months, then adding or intensifying insulin therapy should be considered.

For HbA1c of > 9%:

- In patients without symptoms, dual therapy or triple therapy should be considered.
- In patients with symptoms, insulin ± other agents should be considered.
- For patients with or without symptoms, adding or intensifying insulin should be considered.

SGLT2 inhibitor-specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and systolic blood pressure.
- Empagliflozin is the only SGLT2 inhibitor associated with significantly lower rates of all-cause and CV death and lower risk of HHF. Empagliflozin received FDA-approval for the indication of reduction of cardiac mortality.
- Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, potential hypotension due to increased diuresis, and incidences of bone fractures in patients taking canagliflozin and dapagliflozin. Post-marketing reports of DKA have been reported in T1DM and T2DM with less than expected hyperglycemia (euglycemic DKA).

- ADA Standards of Medical Care in Diabetes – 2017 *(ADA 2017[b])*
  - A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences. Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM.
  - SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in T2DM. None of the available 3 agents are FDA-approved for the treatment of patients with T1DM.
  - The FDA issued a warning about the risk of ketoacidosis occurring in the absence of significant hyperglycemia (euglycemic DKA) in patients with type 1 and type 2 diabetes treated with SGLT2 inhibitors. Symptoms of ketoacidosis include dyspnea, nausea, vomiting, and abdominal pain. Patients should be instructed to stop taking SGLT2 inhibitors and seek medical attention immediately if they have symptoms or signs of ketoacidosis.
  - In patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, empagliflozin or liraglutide should be considered as they have been shown to reduce CV and all-cause mortality when added to standard care.

SAFETY SUMMARY

- Contraindications:
  - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, or empagliflozin.
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Metformin-containing products have the following contraindications:
    - Severe renal impairment (Invokamet, Invokamet XR, Synjardy, Synjardy XR: eGFR < 45 mL/min/1.73 m^2; Xigduo XR: eGFR < 60 mL/min/1.73 m^2), end-stage renal disease, or dialysis

- Known hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including DKA, with or without coma. DKA should be treated with insulin.

○ Linagliptin-containing products have the following contraindications:
- History of hypersensitivity reactions to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticarial, or bronchial hyperreactivity.

○ Saxagliptin-containing products have the following contraindications:
- History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, including anaphylaxis, angioedema or exfoliative skin conditions.
- Moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end-stage renal disease, or dialysis.

• Boxed Warnings:

○ Canagliflozin-containing products carry a Boxed Warning for lower limb amputation. An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed in the CANVAS and CANVAS-R trials in patients with T2DM who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.

○ Metformin-containing products carry a Boxed Warning for lactic acidosis. Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as concomitant use of certain drugs, age > 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and abdominal pain. Laboratory abnormalities include increased lactate/pyruvate ratio, anion gap acidosis, metformin plasma levels generally > 5 mcg/mL, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.

• Warnings and Precautions

○ Several FDA drug safety communications have been issued for canagliflozin over the past year.
- The FDA published a drug safety communication in June 2016 stating that the existing warning about the risk of acute kidney injury for canagliflozin (Invokana, Invokamet, Invokamet XR) and dapagliflozin (Farxiga, Xigduo XR) has been strengthened. Based on recent confirmed cases of acute kidney injury, the warning in the drug label has been revised to include more specific parameters regarding the monitoring of renal function and discontinuation in cases of renal impairment *(FDA Drug Safety Communication 2016[b])*.
- The drug safety communication issued in May 2016 with interim safety results from the CANVAS and CANVAS-R studies has since culminated in a formal boxed warning on all canagliflozin-containing agents for the risk of lower limb amputation *(FDA Drug Safety Communication 2016[a] and 2017)*.
- The FDA issued a drug safety communication regarding the risk of fracture and bone density in 2016.
  - The FDA evaluated the incidence of bone fractures based on a pooled analysis of nine clinical trials (n = 10,194) with patients ages 55 to 80 who had a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of bone fractures were greater with canagliflozin 100 mg and 300 mg vs. placebo or an active comparator (1.4 and 1.5 vs. 1.1 per 100 patient-years of exposure, respectively). Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities *(Watts et al 2016)*.
  - Based on an FDA-required post-marketing trial, canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo over two years in elderly individuals (55 to 80 years of age) with poorly controlled T2DM. Placebo-corrected declines in bone mineral density at the total hip were 0.9% and 1.2%, respectively for canagliflozin 100 mg and 300 mg, and were 0.1% at the femoral neck for both canagliflozin doses. Placebo-adjusted bone mineral density decline at the distal forearm was 0.4% with canagliflozin 300 mg and 0% with canagliflozin 100 mg *(Bilezikian et al 2016, FDA Drug Safety Communication 2015)*.

Table 3. Warnings and Precautions

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
Hypotension: Before initiating therapy, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.	✔	✔	✔	✔	✔	✔	✔	✔
Ketoacidosis: Assess patients who present with signs/symptoms of metabolic acidosis regardless of blood glucose level.	✔	✔	✔	✔	✔	✔	✔	✔
Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.	✔	✔	✔	✔	✔	✔	✔	✔
Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR < 60 mL/min/1.73 m^2. Avoid use of dapagliflozin when eGFR < 60 mL/min/1.73 m^2.	✔	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination.	✔	✔	✔	✔	✔	✔	✔	✔
Macrovascular outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction.	✔	✔		✔	✔	✔	✔	✔
Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia.		✔				✔		
Hypersensitivity reactions: Monitor for anaphylaxis and angioedema. Discontinue use and treat and monitor until signs and symptoms resolve.		✔		✔	✔	✔		
Genital mycotic infections: Monitor and treat if indicated.	✔	✔	✔	✔	✔	✔	✔	✔
Increased LDL-C: Monitor LDL-C and treat per standard of care.	✔	✔	✔	✔	✔	✔	✔	✔
Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with	✔				✔			✔

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
caution in patients with a prior history of bladder cancer.								
Lower limb amputation: An approximately 2-fold increased risk of lower limb amputations was observed with canagliflozin in patients with T2DM who had either established CVD or were at risk for CVD.		✔				✔		
Urosepsis and Pyelonephritis: Evaluate for signs/symptoms of UTI and treat promptly, if indicated.	✔	✔	✔	✔	✔	✔	✔	✔
Bone fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed. Consider factors that contribute to fracture risk before initiating canagliflozin		✔				✔		
Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.						✔	✔	✔
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal pancreatitis. Discontinue if suspected.				✔	✔			
Arthralgia: Severe and debilitating arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate.				✔	✔			
Bullous pemphigoid: Patients taking DPP-4 inhibitors have required hospitalization due to bullous pemphigoid. Patients should report development of blisters or erosions. Discontinue if suspected.				✔	✔			
Heart failure: In a CV outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of HHF was higher in the saxagliptin group (estimated HR: 1.27; 95% CI, 1.07 to 1.51). Subjects with a prior history of heart failure and					✔			

Warnings and Precautions	Single-Entity Products			Combination Products				
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)
subjects with renal impairment had a higher risk for HHF, irrespective of treatment assignment; monitor, observe, and advise patients of this risk and consider discontinuation in any patients that develop signs of heart failure.								
Radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin-containing agents should be withheld at the time of or prior to the procedure (and withheld for 48 hours subsequent to the procedure). They should be reinstituted only after renal function is normal or mildly impaired.						✔	✔	✔

- Adverse effects:
  - The most common adverse effects seen with the SGLT2 inhibitors are genital mycotic infections and urinary tract infections.
  - Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Drug Interactions:

  All SGLT2 Inhibitors:
  - Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
  - Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

  Canagliflozin:
  - Co-administration of canagliflozin with inducers of uridine diphosphate glucuronosyltransferase (UGT) enzymes such as rifampin, phenytoin, phenobarbital, and ritonavir may result in decreased canagliflozin area under the concentration curve (AUC); consider increasing canagliflozin dosage to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.
  - Co-administration of canagliflozin 300 mg with digoxin have been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

  Dapagliflozin:
  - When dapagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:

- Diuretics: Co-administration of diuretics with increased urine volume and frequency of voids may increase the potential for volume depletion.

Linagliptin-containing products:

- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of cytochrome P450 (CYP) 3A4 or P-glycoprotein. Consider alternative treatments.

Saxagliptin-containing products:

- Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors; do not co-administer Qtern with strong CYP3A4/5 inhibitors.

Metformin-containing products:

- Cationic drugs such as cimetidine may reduce metformin elimination and may increase the risk for lactic acidosis. Other drugs which may increase exposure to metformin include ranolazine, vandetanib, and dolutegravir.
- Alcohol may potentiate the effect of metformin on lactate metabolism. Advise against excessive alcohol intake.
- Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving a metformin-containing drug, monitor for hypoglycemia.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Initiation is not recommended if eGFR is < 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 45 to < 60 mL/min/1.73 m^2. Not recommended if eGFR persistently falls below 45 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.
Jardiance (empagliflozin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 45 mL/min/1.73 m^2.
Combination products				
Invokamet (canagliflozin/ metformin)	Tablets	Oral	Two times daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Invokamet XR (canagliflozin/ metformin ER)	Tablets	Oral	Daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Xigduo XR (dapagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m^2). Not recommended in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 60 mL/min/1.73 m^2. Discontinue if eGFR falls persistently below 60 mL/min/1.73 m^2.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2. Discontinue if eGFR is < 45 mL/min/1.73 m^2.
Synjardy (empagliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy.

See the current prescribing information for full details

CONCLUSION

- Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of SGLT2, the co-transporter responsible for the majority of reabsorption of glucose filtered by the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose, lower the renal threshold for glucose, and thereby increase urinary glucose excretion.
- Similar to other currently available oral antidiabetic agents, SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.5% to 1%. They have been studied as monotherapy and in combination with metformin and other antidiabetic agents.

- The SGLT2 inhibitor/metformin combinations include Invokamet/Invokamet XR (canagliflozin/metformin), Synjardy/Synjardy XR (empagliflozin/metformin), and Xigduo XR (dapagliflozin/metformin). Glyxambi (empagliflozin/linagliptin) and Qtern (dapagliflozin/saxagliptin) are SGLT2 inhibitor/DPP-4 inhibitor combination products.
- In clinical trials, the SGLT2 inhibitors have been evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. They have demonstrated effectiveness when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, FPG, weight gain, PPG, and blood pressure when used as monotherapy or in combination therapy.
- SGLT2 inhibitors have additional beneficial effects such as weight reduction and decreases in blood pressure. These beneficial changes are hypothesized to result from either a loss of calories associated with induction of urinary glucose excretion or a reduction in fluid volume through the osmotic diuretic effect. These agents are not associated with hypoglycemia; however, hypoglycemia risk may increase when combined with insulin or an insulin secretagogue.
- All three single-entity SGLT2 inhibitors are dosed once daily. Dapagliflozin is not recommended in patients with an eGFR < 60 mL/min/1.73 m^2. Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m^2. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased LDL-C levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. Warnings for bone fractures and most recently, lower limb amputation were added for canagliflozin-containing products. Warnings for DKA, urosepsis, and pyelonephritis were also added to the labeling of SGLT2 inhibitors after increased incidences were reported post-marketing.
- Consensus guidelines generally recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes.
- Evidence that glucose lowering reduces the rates of CV events and death had not been convincingly shown until the publication of results from the EMPA-REG OUTCOME trial, which was a long-term, placebo-controlled study involving 7020 patients with T2DM at high risk for CV events. When added to standard of care, empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal MI, or nonfatal stroke) by 14% vs. placebo ($p < 0.001$ for non-inferiority; $p = 0.04$ for superiority). In the CANVAS trials, significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs. placebo: 26.9 vs. 31.5 participants with an event per 1000 patient-years (HR: 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority).
- The SGLT2 inhibitors may provide another treatment option for glycemic control in patients unable to tolerate first-line treatment with metformin or other oral antidiabetic therapies due to adverse effects or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin and now most recently with canagliflozin, which suggest that SGLT2 inhibitors may play a significant role in T2DM patients at high risk for CV events; however, the results of an ongoing CV outcomes study with dapagliflozin are still pending. Although the long term effects of SGLT2 inhibition are not known at this time, clinical studies demonstrate that the benefits outweigh the risks.

REFERENCES

- American Diabetes Association. Diabetes Basics: Type 2 (2017[a]). http://www.diabetes.org/diabetes-basics/type-2/?loc=util-header_type2. Accessed July 31, 2017.
- American Diabetes Association. Standards of Medical Care in Diabetes – 2017. Diabetes Care. 2017[b];40(suppl 1):S1-S135 http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf. Accessed July 31, 2017.
- Araki E, Tanizawa Y, Tanaka Y, et al. Long-term treatment with empagliflozin as add-on to oral anti-diabetes therapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17(7):665-74.
- Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-2233.
- Bailey CJ, Iqbal N, T'Joen C, et al. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes Obes Metab. 2012;14(10):951-959.
- Bailey CJ, Morales-Villegas EC, Woo, V, et al. Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabet Med. 2015;32:531-41.
- Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomize, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2(5):369-84.

- Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with Type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab. 2016;101(1):44-51.
- Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab. 2015;17:294-303.
- Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract. 1995;41:72-84.
- Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, Wilson LM, Chu Y, Iyoha E, Maruthur NM. Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 16-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed July 31, 2017.
- Cefalu W, Leiter L, Yoon KH L, et al. Efficacy and safety of canagliflozin vs glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;182-941-950.
- Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report; 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Updated July 17, 2017. Accessed July 31, 2017.
- ClinicalTrials.gov Web site. http://clinicaltrials.gov/. Accessed July 31, 2017.
- Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics. 2013;131:364-382.
- Davies MJ, Trujillo A, Vijapurkar U, et al. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015;17:426-429.
- DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38:384-393.
- Del Prato S, Nauck M, Duran-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin vs a sulphonylurea as add-on therapy to metformin in type 2 diabetes patients: 4-year data. Diabetes Obes Metab. 2015;17(6):581-90.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 31, 2017.
- Farxiga Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. March 2017.
- FDA Drug Safety Communications. Canagliflozin (Invokana, Invokamet): Drug Safety Communication – Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. May 18, 2016[a]. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm501565.htm. Accessed July 31, 2017.
- FDA Drug Safety Communications. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). May 16, 2017. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf. Accessed July 24, 2017.
- FDA Drug Safety Communications. FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. September 10, 2015. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM461790.pdf. Accessed July 25, 2017.
- FDA Drug Safety Communications. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). June 14, 2016[b]. http://www.fda.gov/drugs/drugsafety/ucm505860.htm. Accessed July 31, 2017.
- Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36(12):4015-21.
- Ferrannini E, Jimenez Ramos S, Salsali A, Tang W, List J. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. Diabetes Care. 2010;33:2217-2214.
- Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab. 2014;16(5):467-77.
- Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. Diabetes Ther. 2015 Sep;6(3):289-302.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Rosenblit PD, Umpierrez GE. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. Endocr Pract. 2017 Feb;23(2):207-238.
- Glyxambi prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. March 2017.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37:1650-9.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2013;36:3396-3404.
- Henry RR, Murray AV, Marmolejo MH, Hennicken D, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. Int J Clin Pract. 2012;66:446-456.
- Inagaki N, Kondo K, Yoshinari T, et al. Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. Expert Opin Pharmacother 2014;15:1501-1515.
- Invokamet prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Invokamet XR prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Invokana prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. July 2017.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015;38(1):140-149. http://care.diabetesjournals.org/content/38/1/140.full.pdf+html. Accessed July 31, 2017.
- Jabbour A, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50.
- Jardiance prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.

- Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014 Apr;85(4):962-71.
- Kosiborod M, Cavender MA, Fu AZ, et al.; CVD-REAL Investigators and Study Group*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017 Jul 18;136(3):249-259.
- Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther. 2015 Aug;37(8):1773-88.
- Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2014;16:147-58.
- Lavalle-Gonzalez, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomized trial. Diabetologia. 2013;56:2582-2592.
- Leiter LA, Cefalu WT, Tjerk W, et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62:1252-62.
- Leiter, LA, Yoon HK, Arias P et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38(3):355-64.
- Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16:984-993.
- Matthaei S, Aggarwal N, Garcia-Hernandez P, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes Obes Metab. 2016;18(11):1128-1133.
- Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015;38:365-372.
- Matthaei S, Catrinoiu D, Celiński A, et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. Diabetes Care. 2015;38(11):2018-24.
- Mathieu C, Herrera Marmolejo M, González González JG, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. Diabetes Obes Metab. 2016;18(11):1134-1137.
- Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care. 2015;38(11):2009-17.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diabetic Kidney Disease: What is diabetic kidney disease? 2017. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/diabetic-kidney-disease. Updated February 2017. Accessed July 31, 2017.
- Nauck MA, Del Prato S, Duran-Garcia A, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizde as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab. 2014;16(11):1111-20.
- Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. Diabetes Care. 2011;34:2015-2022.
- Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925. [Epub ahead of print]
- Neal B, Perkovic V, de Zeeuw D et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015;38:403-411.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 31, 2017.
- Orme M, Fenici P, Duprat-Lomon I, et al. A systematic review and mixed-treatment comparison of dapagliflozin with existing anti-diabetes treatments for those with type 2 diabetes mellitus inadequately controlled by sulfonylurea monotherapy. Diabetol Metab Syndr. 2014 Jun 11;6:73.
- Ptaszynska A, Johnsson KM, Parikh SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf. 2014;37(10):815-29.
- Qtern prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. February 2017.
- Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomized, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endrocrinol. 2014;2:691-700.
- Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1(3):208-19.
- Rosenstock J, Chuck L, Gonzalez-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naïve type 2 diabetes. Diabetes Care. 2016;39(3):353-62.
- Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care. 2015[a];38:376-83.
- Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care. 2014;37:1815-23.
- Rosenstock J, Jelaska A, Zeller C, et al for the EMPA-REG BASALTM trial investigators. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015[b] Oct;17(10):936-48.
- Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013;15:1154-60.
- Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473-1478.
- Ross S, Thamer C, Cescutti J, et al. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2015;17:699-702.

- Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care. 2013;36:2508-2515.
- Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open. 2016 Feb 24;6(2):e009417.
- Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocrine Disorders. 2014;14:37.
- Sinclair AJ, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in individuals aged 75 and older with Type 2 Diabetes Mellitus: A pooled analysis. J Am Geriatr Soc. 2016;64:543-552.
- Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15(4):372-82.
- Strojek K, Yoon KH, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13:928-938.
- Strojek K, Yoon KH, Hruba V, et al. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. Diabetes Ther. 2014;5:267-83.
- Supplement to: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. DOI: 10.1056/NEJMoa1611925.
- Sun Y, Zhou Y, Chen X et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. BMJ Open. 2014 Apr 7;4(4):e004619.
- Synjardy prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.
- Synjardy XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2016.
- Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-334.
- Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2016;101(1):157-166.
- Weir MR, Januszewicz A, Gilbert RE et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. J Clin Hypertens. 2014;16:875-882.
- Wilding J, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea. Int J Clin Pract. 2013;67:1267-1282.
- Wilding JP, Woo V, Soler N, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. Ann Intern Med. 2012;156:405-415.
- Xigduo XR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. March 2017.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;14:463-479.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2014;16:1016-1027.
- Yang XP, Lai D, Zhong XY, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol. 2014;70:1149-1158.
- Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016 Aug;18(8):783-94.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.

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Therapeutic Class Overview
Bone Density Regulators

INTRODUCTION

- Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture (Cosman et al, 2014). The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have osteoporosis and more than 2 million osteoporosis-related fractures occur annually, with more than 70% of these occurring in women. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (Camacho et al, 2016).
- According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score (World Health Organization, 1994).
- Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis, and low bone mass is the primary indicator of fracture risk (Watts et al, 2010). Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death (Cosman et al, 2014).
- To decrease the risk of fractures, the general population should be advised to consume 1,200 mg of calcium and 800 to 1,000 mg of vitamin D per day from dietary sources or supplements. All individuals should also participate in regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Strategies for preventing falls should be implemented when needed. Smoking cessation and avoidance of excessive alcohol intake are other initiatives to prevent osteoporosis (Camacho et al, 2016; Cosman et al, 2014).
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- Bisphosphonates are used to prevent and treat postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. There are several bisphosphonates approved for treatment of Paget's disease and malignancy-induced bone conditions, but not for osteoporosis. These agents include AREDIA® (pamidronate), DIDRONEL® (etidronate), and ZOMETA® (zoledronic acid), which will not be discussed in this review (Micromedex 2.0®, 2017).
- Other agents used to treat postmenopausal osteoporosis include calcitonin (MIACALCIN®), an estrogen agonist/antagonist (EVISTA®), the parathyroid hormone analogs (FORTEO® and TYMLOS™) and receptor activator of nuclear factor K-B ligand inhibitor (PROLIA®). These agents also have other indications such as reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis, reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer, increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, treatment of Paget's disease, treatment of hypercalcemia, treatment of glucocorticoid-induced osteoporosis at high risk of fracture, treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer, and treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Other agents in the estrogen agonist/antagonist class include CLOMID® or SEROPHENE® (clomiphene), tamoxifen, FARESTON® (toremifene) and OSPHENA® (ospemifene). These agents have different indications including: to induce ovulation in appropriately selected anovulatory women desiring pregnancy; the treatment and prevention of breast cancer; and treatment of women experiencing moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause (Micromedex 2.0, 2017). These agents are not approved for treatment of osteoporosis and will not be discussed in this review.
- Another agent in the receptor activator of nuclear factor K-B ligand inhibitor class is XGEVA® (denosumab). It is approved to prevent skeletal-related events in patients with bone metastases from solid tumors, treat hypercalcemia of malignancy refractory to bisphosphonates, and treat adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (Micromedex 2.0, 2017). It will not be further discussed in this review.
- The Food and Drug Administration (FDA) has approved estrogen/hormone therapy for the prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. The Women's Health Initiative (WHI) found that five years of hormone therapy in the form of PREMPRO® (conjugated estrogen/medroxyprogesterone) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (Writing Group, 2002). However, the study also reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis during five years of treatment

(Writing Group, 2002). It is now recommended to use estrogen/hormone therapy in the lowest doses for the shortest duration. Thus, these agents are not recommended for long-term prevention and will not be further discussed in this review.

- Medispan Class: Bone Density Regulators; Hormone Receptor Modulators

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Bisphosphonates			
ACTONEL® (risedronate)	Warner Chilcott	03/27/1998	✔
ATELVIA® (risedronate, delayed release tablet)	Warner Chilcott	10/08/2010	✔
BINOSTO™ (alendronate, effervescent tablet)	Mission	03/12/2012	-
BONIVA® (ibandronate)	Genentech (Roche)	Tablet: 05/24/2005 Injectable: 01/06/2006	✔
FOSAMAX®* (alendronate)	Merck	Tablets: 09/29/1995 Oral Soln: 09/17/2003*	✔
FOSAMAX PLUS D® (alendronate/ cholecalciferol)	Merck	04/07/2005	-
RECLAST® (zoledronic acid)	Novartis	04/16/2007	✔
Calcitonin			
MIACALCIN (calcitonin salmon synthetic)	Novartis	Nasal Spray: 08/17/1995† Injectable: 03/29/1991	✔ -
Estrogen Agonist-Antagonist			
EVISTA (raloxifene)	Eli Lilly	12/09/1997	✔
Parathyroid Hormone Analogs			
FORTEO (teriparatide)	Eli Lilly	06/25/2008	-
TYMLOS (abaloparatide)	Radius Health	04/28/2017	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
PROLIA (denosumab)	Amgen	06/01/2010	-

*Brand FOSAMAX oral solution is not currently marketed; however, a generic is available.
†Brand MIACALCIN nasal spray is not currently marketed; however, a generic is available.
(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	ACTONEL* (risedronate)	ATELVIA* (risedronate)	BINOSTO* (alendronate)	BONIVA* (ibandronate)	FOSAMAX* (alendronate) FOSAMAX PLUS D (alendronate/ cholecalciferol)	RECLAST* (zoledronic acid)
Treatment of postmenopausal osteoporosis	✔	✔	✔	✔	✔	✔
Prevention of postmenopausal osteoporosis	✔			✔ (tablets only)	✔ (FOSAMAX only)	✔
Treatment to increase bone mass in men with osteoporosis	✔		✔		✔	✔
Treatment of glucocorticoid-induced osteoporosis	✔				✔ (FOSAMAX only)	✔
Prevention of glucocorticoid-induced osteoporosis	✔					✔
Treatment of Paget's disease	✔				✔ (FOSAMAX only)	✔

*Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of ACTONEL, BINOSTO, RECLAST and BONIVA for the treatment of osteoporosis are based on clinical data of three years duration. The safety and effectiveness of ATELVIA for the treatment of osteoporosis are based on clinical data of one year duration. The safety and effectiveness of FOSAMAX/FOSAMAX PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after three to five years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

(Prescribing Information: ACTONEL, 2015; ATELVIA, 2015; BINOSTO, 2016; BONIVA, 2016; FOSAMAX, 2015; FOSAMAX PLUS D, 2016; RECLAST, 2017)

Table 3: FDA Approved Indications for Calcitonins, Estrogen Agonist-Antagonist, Parathyroid Hormone Analogs, and Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

Indication	MIACALCIN (calcitonin salmon synthetic)	EVISTA (raloxifene)	FORTEO (teriparatide)	PROLIA (denosumab)	TYMLOS (abaloparatide)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause	✔ †				
Treatment of postmenopausal osteoporosis		✔			
Treatment of postmenopausal osteoporosis at high risk of fracture			✔	✔	✔
Prevention of postmenopausal osteoporosis		✔			
Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis		✔			
Reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer		✔			

Indication	MIACALCIN (calcitonin salmon synthetic)	EVISTA (raloxifene)	FORTEO (teriparatide)	PROLIA (denosumab)	TYMLOS (abaloparatide)
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture			✔		
Treatment of Paget's disease	✔ (injection only)				
Treatment of hypercalcemia	✔ (injection only)				
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture			✔		
Treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer				✔	
Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✔	
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✔	

(Prescribing Information: EVISTA, 2011; FORTEO, 2016; MIACALCIN nasal spray, 2014; MIACALCIN injection, 2016; PROLIA, 2017; TYMLOS, 2017)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Bisphosphonates

- Clinical trials for bisphosphonates included within this review evaluate their efficacy in increasing BMD and/or decreasing bone turnover markers (BTMs). Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD and reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focus on the same therapeutic outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.
- Head-to-head trials have resulted in conflicting data when comparing one bisphosphonate agent to another in regard to efficacy. Data from trials specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk, in both men and women, of developing fractures in both vertebral and non-vertebral areas, compared to placebo (Black et al, 1996; Kanis et al, 2005; Lyles et al, 2007; Ringe et al, 2009; Sawka et al, 2005). Evidence suggests that alendronate results in greater increases of BMD when compared to risedronate (Bonnick et al, 2006; Reid et al, 2006; Reid et al, 2008). Trials also support that risedronate results in a greater reduction in the risk of non-vertebral and hip fractures when compared to alendronate (Silverman et al, 2007). Additionally, there are data to support alendronate and risedronate having similar efficacy (Sarioglu et al, 2006). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over one year in one study with postmenopausal women with osteoporosis and over two years in a study of men with osteoporosis (McClung et al, 2007; Orwoll et al, 2010). Ibandronate has also been shown to reduce vertebral fractures more than alendronate and risedronate in one trial; while two other trials showed ibandronate to be similar in efficacy to alendronate (Guanabens et al, 2013; Harris et al, 2009; Miller et al, 2008[a]). The included data also show that alendronate, risedronate, and zoledronic acid are effective in patients with glucocorticoid-induced osteoporosis (Mok et al, 2008; Okada et al, 2008; Reid et al, 2009). Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. One such trial demonstrated that zoledronic acid is more effective than risedronate, for the treatment of Paget's disease (Reid et al, 2005). Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.
- In terms of safety, one meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events concluded that zoledronic acid had a higher probability of any GI adverse event and nausea. However, risedronate had more serious GI adverse events, and alendronate had more upper GI and esophageal adverse events. Ibandronate was not included in the analysis (Tadrous et al, 2014).

- BINOSTO effervescent 70 mg tablets have been shown to be bioequivalent to alendronate 70 mg tablets. Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week.

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin, as trials are typically small in size and observational in design (Cadarette et al, 2008; Chestnut et al, 2000; Cranney et al, 2002[b]; Downs et al, 2000; Hwang et al, 2006; Kanis et al, 1974; Woodhouse et al, 1977).
- Injectable MIACALCIN (calcitonin-salmon) has demonstrated beneficial effects in the treatment of Paget's disease. Treatment produced bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, injectable MIACALCIN (calcitonin-salmon) has been shown to cause disease regression in some patients (Kanis et al, 1974; Woodhouse et al, 1977).
- Nasal calcitonin-salmon achieved significant increases in BMD at the lumbar spine compared to placebo after six months of therapy, which was maintained for up to two years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement (Chestnut et al, 2000; Downs et al, 2000). Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonins significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for non-vertebral fractures (Hwang et al, 2006).

Estrogen Agonist-Antagonist

- Several placebo-controlled trials have demonstrated that treatment with raloxifene in postmenopausal women with osteoporosis significantly increases BMD. In addition, raloxifene demonstrated beneficial effects on lipid profile parameters (Eastell et al, 2009; Ettinger et al, 1999; Kung et al, 2003; Johnston et al, 2000; Siris et al, 2005; Tanaka et al, 2011). In the MORE trial, raloxifene decreased the risk of vertebral fractures compared to placebo, with no observed difference in the rate of non-vertebral fractures (Kung et al, 2003). There was also no difference in non-vertebral fracture rate during a seven year follow-up of the MORE trial (Siris et al, 2005). These data are supported by results of a meta-analysis of seven placebo-controlled trials, in which the reduction in the risk of vertebral fractures associated with raloxifene was inconsistent between two clinical trials, and neither trial demonstrated a reduction in the risk in non-vertebral fractures (Eastell et al, 2009). When compared to bisphosphonate therapy, increases in BMD were significantly greater with alendronate compared to raloxifene (Recker et al, 2007).
- In addition to evaluating the efficacy of raloxifene on bone, the MORE trial evaluated its efficacy in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. As a secondary end point, raloxifene reduced the incidence of newly diagnosed invasive breast cancer compared to placebo (Cummings et al, 1999). In addition, the CORE trial evaluated the efficacy of four additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of eight years, the incidence of invasive breast cancer and estrogen receptor-positive breast cancer was reduced by 66% and 76%, respectively, with raloxifene compared to placebo. Furthermore, the incidence of noninvasive breast cancer in women receiving raloxifene was similar to that in women receiving placebo (Martino et al, 2004). The placebo-controlled RUTH trial supports the findings of the MORE trial in that raloxifene significantly reduced the risk of invasive breast cancer, as well as vertebral fractures, and did not significantly affect the risk of coronary heart disease. Raloxifene, however, was associated with a higher risk of venous thromboembolism and fatal stroke (Barrett-Connor et al, 2006).
- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the two treatments (Vogel et al, 2006). However, in a follow-up trial of 6.75 median years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was still no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years (Vogel et al, 2010).
- In terms of safety data, raloxifene was most commonly associated with hot flashes and leg cramps. Several clinical trials reported thromboembolic events (Bachmann et al, 2011; Barrett-Conner et al, 2006; Cadarette et al, 2008; Cranney et al, 2002[a]; Cummings et al, 1999; Eastell et al, 2009; Ensrud et al, 2006; Ettinger et al, 1999; Kung et al, 2003; Johnston et al, 2000; Martino et al, 2004; Recker et al, 2007; Siris et al, 2005; Tanaka et al, 2011; Vogel et al, 2006; Vogel et al, 2010).

Parathyroid Hormone Analogs

- A two year, placebo-controlled trial (N=437) evaluating FORTEO (teriparatide) in increasing bone mass in men with primary or hypogonadal osteoporosis was terminated early when a long-term toxicology trial noted an increase in the incidence of osteosarcoma in rats receiving FORTEO (teriparatide). After a median duration of 11 months, FORTEO (teriparatide) significantly increased BMD at the lumbar spine and femoral neck compared to placebo (Orwoll et al, 2003). In a follow-up of this trial, no serious safety concerns with FORTEO (teriparatide) were observed (Kaufman et

al, 2005). FORTEO (teriparatide) has also been compared to the bisphosphonate alendronate for the treatment of men with primary or hypogonadal osteoporosis. Specifically, when compared to alendronate and the combination of FORTEO (teriparatide) and alendronate, FORTEO (teriparatide) significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (Finkelstein et al, 2003).

- FORTEO (teriparatide) also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. In addition, after 36 months, significantly fewer patients receiving FORTEO (teriparatide) had a vertebral fracture (Langdahl et al, 2009; Saag et al, 2007; Saag et al, 2009). FORTEO (teriparatide) was also compared to risedronate in men with glucocorticoid-induced osteoporosis. At 18 months, teriparatide was more effective at increasing BMD at the lumbar spine than risedronate (Gluer et al, 2013).
- FORTEO (teriparatide) has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women (Body et al, 2002; Cosman et al, 2009; Cosman et al, 2011; Eastell et al, 2009; Hwang et al, 2006; Lindsay et al, 2004; McClung et al, 2005; Minne et al, 2008; Neer et al, 2001; Obermayer-Pietsch et al, 2008). The EUROFORS trial was a prospective, two year trial in which all patients received FORTEO (teriparatide) for the first year of treatment. After 12 months, patients were divided into two different substudies. In Substudy 1, for the second year of treatment, patients were randomized to FORTEO (teriparatide), the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on FORTEO (teriparatide) for the second year of treatment. After the first year of treatment, FORTEO (teriparatide) significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of FORTEO (teriparatide) appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued FORTEO (teriparatide) for a total of two years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of treatment, BMD at the lumbar spine, total hip, and femoral neck continued to increase significantly with FORTEO (teriparatide). BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significantly increased BMD at the femoral neck (Eastell et al, 2009; Minne et al, 2008; Obermayer-Pietsch et al, 2008). In addition to significant increases in BMD, placebo-controlled trials demonstrate that FORTEO (teriparatide) significantly reduces the risk of vertebral and non-vertebral fractures (Body et al, 2002; Lindsay et al, 2004; Neer et al, 2001). Data also suggest that FORTEO (teriparatide) in combination with a bisphosphonate may result in significant increases in BMD compared to monotherapy with either FORTEO (teriparatide) or a bisphosphonate (Cosman et al, 2009; Cosman et al, 2011). In another study of 12 months duration, combination teriparatide and denosumab were compared to either treatment alone. Combined teriparatide and denosumab increased BMD at the posterior-anterior (PA) spine, femoral neck, and hip significantly more than either drug alone (Leder et al, 2014; Tsai et al, 2013).
- In terms of safety data, no clinically significant concerns related to FORTEO (teriparatide) were observed; however, treatment was associated with a higher rate of hypercalcemia compared to placebo and bisphosphonate therapy. No cases of osteosarcoma were reported (Body et al, 2002; Cosman et al, 2009; Cosman et al, 2011; Eastell et al, 2009; Finkelstein et al, 2003; Finkelstein et al, 2006; Hwang et al, 2006; Kaufman et al, 2005; Langdahl et al, 2009; Lindsay et al, 2004; McClung et al, 2005; Minne et al, 2008; Neer et al, 2001; Obermayer-Pietsch et al, 2008; Orwoll et al, 2003; Saag et al, 2007; Saag et al, 2009).
- The efficacy of TYMLOS (abaloparatide) was compared with FORTEO (teriparatide) and placebo in the 18-month randomized controlled ACTIVE trial in 2,463 postmenopausal women with osteoporosis. Treatment with TYMLOS (abaloparatide) resulted in a significant reduction in new morphometric vertebral and nonvertebral fractures vs placebo, while treatment with teriparatide also resulted in a significant reduction in new morphometric vertebral fractures vs placebo. For reduction in nonvertebral fractures, treatment with abaloparatide was not statistically different vs teriparatide. The incidence of hypercalcemia was significantly lower with abaloparatide vs teriparatide (Miller et al, 2016). The ACTIVExtend open-label extension trial evaluated 6 months of follow-up therapy with alendronate 70 mg once weekly in both the TYMLOS (abaloparatide) and placebo groups, and demonstrated that the treatment cycle with abaloparatide for 18 months followed by alendronate reduced new morphometric vertebral fractures by 87%, nonvertebral fractures by 52%, clinical fractures by 45%, and major osteoporotic fractures by 58% vs placebo and alendronate (Cosman et al, 2017).

Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

- The safety and efficacy of PROLIA (denosumab) for the treatment of bone loss in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer were established in a two year, double-blind, placebo-controlled, randomized trial enrolling 252 women (Ellis et al, 2008). Patients were randomized to denosumab SC every six months (n=127) or placebo (n=125) for a total of four doses; all patients received supplemental calcium and vitamin D. Overall, denosumab increased BMD at the lumbar spine at 12 and 24 months by 5.5% and 7.6% compared to placebo (P<0.0001 at both time points). BMD at the lumbar spine bone was significantly higher with PROLIA (denosumab) compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95%

confidence interval [CI], 4.8 to 6.3; P<0.0001). Furthermore, after two years, PROLIA (denosumab) increased BMD at the lumbar spine (-1.4% placebo, +4.8% denosumab), total hip (-1.0% placebo, +3.8% denosumab), and femoral neck (-0.8% placebo, +2.8% denosumab).

- A double-blind, placebo-controlled, Phase 3 trial evaluated denosumab vs placebo in 3,420 postmenopausal women with early hormone-receptor positive breast cancer receiving treatment with aromatase inhibitors (Gnant et al, 2015). Women were randomized to denosumab 60 mg every six months or placebo. The time to first fracture, the primary outcome measure, was significantly delayed in the denosumab group compared to placebo (hazard ratio [HR] 0.50; 95% CI, 0.39 to 0.65; P<0.0001). The incidence of adverse events was similar in both treatment groups.
- When compared to placebo, PROLIA (denosumab) significantly prolonged bone-metastasis-free survival (composite of time to first occurrence of bone metastasis and death from any cause) in men with non-metastatic prostate cancer (treatment difference, 4.2 months; HR 0.85; 95% CI, 0.73 to 0.98; P=0.028). There was no difference in overall survival observed between the two treatments. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with PROLIA (denosumab) compared to placebo (P<0.001 for all). Of note, the FDA-approved dosing was not evaluated in this trial; PROLIA (denosumab) was administered once monthly (Smith et al, 2012). The ADAMO trial showed that denosumab therapy administered every six months continued to increase BMD in men with low BMD throughout the second year of treatment (Langdahl et al, 2015).
- Of the available clinical trial data evaluating the safety and efficacy of PROLIA (denosumab) in postmenopausal women with osteoporosis who are at high risk of fracture, only one placebo-controlled trial (the FREEDOM trial) demonstrated a reduction in the risk of fracture with PROLIA (denosumab). In this trial, after 36 months, there were significant reductions with PROLIA (denosumab) compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk, 0.32; 95% CI, 0.26 to 0.41; P<0.001), non-vertebral (6.5% vs 8%; relative risk, 0.80; 95% CI, 0.67 to 0.95; P=0.01), and hip fractures (0.7% vs 1.29%; relative risk, 0.6; 95% CI, 0.31 to 0.97; P=0.04)(Cummings et al, 2009). A three-year extension trial maintained the denosumab patients on active treatment for a total of six years and crossed-over the placebo patients to denosumab treatment for a total of three years. For patients on denosumab for six years, BTMs were maintained at lower than pretreatment levels and BMD continued to increase. Fracture incidence in the long-term group remained low and below the rates reported in the FREEDOM placebo group. For the cross-over group, data obtained were consistent with FREEDOM observations: rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, and a favorable benefit/risk profile (Bone et al, 2013).
- A meta-analysis/systematic review of clinical trials of PROLIA (denosumab) in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of PROLIA (denosumab) on BTMs and BMD. In this analysis, adverse events, including fracture risk, were also evaluated as secondary endpoints. Due to missing or unavailable data, it was not possible for the investigators to evaluate the efficacy of PROLIA (denosumab) based on change in baseline BMD. Despite this, it was observed that treatment with PROLIA (denosumab) was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, it was revealed that PROLIA (denosumab) was not associated with a significant reduction in fracture risk (odds ratio, 0.74; 95% CI, 0.33 to 0.64; P=0.45) (Anastaskilakis et al, 2009).
- The efficacy of PROLIA (denosumab) at increasing BMD is also supported by three dose-ranging, placebo-controlled trials, as well as a head-to-head trial with the bisphosphonate, alendronate (Brown et al, 2009; Lewiecki et al, 2007; McClung et al, 2006; Miller et al, 2008[b]). The three dose-ranging trials followed patients for a total of 48 months. In the final trial, it was demonstrated that after 48 months PROLIA (denosumab) significantly increased BMD at all measured skeletal sites (lumbar spine, total hip, and distal 1/3 radius) (P<0.001), and achieved potent and sustained reductions of BTMs compared to placebo (Cummings et al, 2009). In a small subset of patients who discontinued treatment with PROLIA (denosumab), it was observed that subsequent decreases in BMD at measured skeletal sites occurred. When compared to alendronate, changes in BMD at the total hip were also significantly greater with PROLIA (denosumab) at 12 months (3.5% vs 2.6%; P<0.0001) (Brown et al, 2009). In a second meta-analysis comparing PROLIA (denosumab) to weekly alendronate, no difference in fracture risk was demonstrated (odds ratio, 1.42; 95% CI, 0.84 to 2.40; P=0.19); however, both treatments were associated with significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after six months (Lin et al, 2012). In a 12-month trial comparing denosumab to monthly ibandronate therapy, denosumab treatment resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate therapy (Recknor et al, 2013).
- In terms of safety data, no clinically significant concerns related to PROLIA (denosumab) were observed; the safety profile of PROLIA (denosumab) appears similar to that of bisphosphonates (Anastaskilakis et al, 2009; Brown et al, 2009; Cummings et al, 2009; Lewiecki et al, 2007; Lin et al, 2012; McClung et al, 2006; Miller et al, 2008[b]; Smith et al, 2012).

Comparative Efficacy

- From the Agency for Healthcare Research and Quality (AHRQ) evaluation (Crandall et al, 2012), the following conclusions were reached:
    - Calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis.
    - There is a high level of evidence from randomized controlled trials (RCTs) that BINOSTO (alendronate effervescent tablet), alendronate, risedronate, ibandronate, zoledronic acid, PROLIA (denosumab), FORTEO (teriparatide), and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
    - There is a high level of evidence from RCTs that BINOSTO (alendronate effervescent tablet), alendronate, risedronate, zoledronic acid and PROLIA (denosumab) reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that FORTEO (teriparatide) reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
    - There is a high level of evidence from RCTs that BINOSTO (alendronate effervescent tablet), alendronate, risedronate, zoledronic acid, and PROLIA (denosumab) reduce the risk of hip fractures in postmenopausal women with osteoporosis.
    - There is insufficient evidence from head-to-head trials with bisphosphonates to support the superiority of one agent over the others for the prevention of fractures.
    - The evidence is insufficient regarding the use of combinations of osteoporosis therapies or sequential use of osteoporosis therapies in relation to fracture outcomes.
    - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men.
    - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies.
    - About half of patients appeared to show persistence with osteoporosis treatment at one year.
    - Adverse effects of concern identified from the report included the following:
        - A relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
        - Evidence is high for an increased risk for venous thromboembolic events (eg, pulmonary embolism) and vasomotor flushing (hot flashes) with raloxifene therapy.
        - Evidence is insufficient regarding the risk of esophageal cancer with bisphosphonates.
        - Evidence is high regarding the risk for alendronate and mild upper gastrointestinal events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn).
        - Evidence is high that the prevention and treatment of osteoporosis with bisphosphonates remains a relatively minor contributor to the development of osteonecrosis of the jaw.
        - The risk remains low for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis compared with the numbers of osteoporotic fractures prevented by bisphosphonate therapy.
        - Evidence is high for rashes, injection site reactions, and infection with PROLIA (denosumab).
- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In two clinical trials, bisphosphonate and parathyroid hormone analog therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon (Downs et al, 2000; Hwang et al, 2006).
- A network meta-analysis found that zoledronic acid significantly increased BMD in lumbar spine and teriparatide decreased fracture rates in men with osteoporosis when compared to other agents such as alendronate, ibandronate, and risedronate (Chen et al, 2015).
- A network meta-analysis performed indirect comparisons to determine the likelihood that each drug would be the most preferable for various outcomes (Yang et al, 2016). Among products included in this review, the most preferred agents for various outcomes were FORTEO (teriparatide) in non-vertebral fractures; PROLIA (denosumab), zoledronic acid, and alendronate in hip fractures; FORTEO (teriparatide) in wrist fractures; and raloxifene, alendronate, and PROLIA (denosumab) for adverse events.
- A systematic review and meta-analysis demonstrated FORTEO (teriparatide) to be superior vs alendronate for increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the percentage change in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the two therapies (Wang et al, 2017).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of three RCTs to evaluate the comparative safety and efficacy of teriparatide, abaloparatide, and zoledronic acid for treatment of osteoporosis in postmenopausal women at high risk for fracture The analysis determined that teriparatide and abaloparatide were not significantly different from each other or zoledronic acid in reducing morphometric vertebral or nonvertebral fractures, and safety issues had little influence on the net benefit for each therapy compared to each other (CTAF, 2017).

- A systematic review and meta-analysis demonstrated significantly lower risk of vertebral fractures with alendronate and risedronate in men with osteoporosis, but not with injectable calcitonin or denosumab vs controls. For bisphosphonates as a treatment category, meta-analyses demonstrated significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (Nayak & Greenspan, 2017).

SAFETY SUMMARY

- Contraindications
  - Bisphosphonates
    - Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
    - Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for BONIVA)
    - Hypocalcemia
  - FOSAMAX oral solution should not be administered to patients at increased risk of aspiration
  - EVISTA
    - Active or past history of venous thromboembolism
    - Pregnancy or nursing mothers
  - PROLIA
    - Hypocalcemia
    - Pregnancy or nursing mothers
- Warnings/precautions
  - Bisphosphonates
    - Caution should be used in patients with active gastrointestinal problems (except RECLAST).
    - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
    - Osteonecrosis of the jaw; can occur spontaneously. Risk factors include dental procedures, cancer diagnosis, poor oral hygiene, medications such as chemotherapy agents, corticosteroids, and angiogenesis inhibitors, or certain co-morbidities (dental disease, anemia, coagulopathy, and infection).
    - Caution should be used in aspirin sensitive patients (RECLAST).
    - Caution should be used in patients who must restrict sodium intake (BINOSTO).
  - EVISTA
    - **Boxed warning:** Increased risk of venous thromboembolism and death from stroke
    - Venous thromboembolism: increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.
    - Treatment with EVISTA should be discontinued 72 hours prior to and during prolonged immobilization.
    - Death due to stroke: increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen in this trial. Risk-benefit balance should be considered in women at risk for stroke.
    - Cardiovascular disease: EVISTA should not be used for the primary or secondary prevention of cardiovascular disease.
    - Treatment with EVISTA is not recommended in premenopausal women
    - Caution should be used in patients with hepatic impairment.
    - Concomitant use with systemic estrogens is not recommended.
    - Hypertriglyceridemia: If previous treatment with estrogen resulted in hypertriglyceridemia, serum triglycerides should be monitored.
  - FORTEO and TYMLOS
    - **Boxed warning:** FORTEO should not be used in patients at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, prior external beam or implant radiation involving the skeleton, , and in pediatric and young adult patients with open epiphyses).
    - **Boxed warning**: TYMLOS should not be used in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. Cumulative use of TYMLOS and parathyroid hormone analogs (eg, teriparatide) > 2 years during a patient's lifetime is not recommended.

        - Orthostatic hypotension: Patients should be instructed to sit or lie down if symptoms develop after dose administration with TYMLOS; transient orthostatic hypotension may occur with initial doses of FORTEO.
        - Caution should be used in patients with active or recent urolithiasis; urinary calcium should be monitored.
        - TYMLOS should not be used in patients with hypercalcemia or hypercalcemic disorders; FORTEO may increase serum calcium, urinary calcium, and serum uric acid.
        - FORTEO should not be used > 2 years during a patient's lifetime.
    - MIACALCIN
        - Potential increased risk of malignancies in calcitonin-salmon-treated patients. The benefits for the individual patient should be carefully considered against possible risks.
        - Circulating antibodies and abnormal urine sediment have been reported with MIACALCIN.
        - Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur (MIACALCIN nasal spray only).
    - PROLIA
        - Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported.
        - Osteonecrosis of the jaw; can occur spontaneously. Risk factors consist of dental procedures, cancer diagnosis, poor oral hygiene, medications such as chemotherapy agents, corticosteroids, and angiogenesis inhibitors, or certain co-morbidities (dental disease, anemia, coagulopathy, and infection). A dental examination is recommended prior to the initiation of PROLIA.
        - Severe musculoskeletal pain has been reported with PROLIA.
        - An increased risk for multiple vertebral fractures has been reported following discontinuation of PROLIA therapy.
        - Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections with PROLIA. The benefit-risk profile should be considered in such patients.
- Adverse events
    - Bisphosphonates
        - The most common adverse effects are headache and gastrointestinal effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.
    - EVISTA
        - The most common adverse events (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating.
    - FORTEO
        - The most common adverse events (> 10%) include nausea, arthralgia, and pain.
    - MIACALCIN
        - The most common adverse events (≥ 3%) with MIACALCIN nasal spray include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
        - The most common adverse events with MIACALCIN injection include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).
    - PROLIA
        - The most common adverse events (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has also been reported in clinical trials.
    - TYMLOS
        - The most common adverse events (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.
- Drug Interactions
    - Bisphosphonates
        - Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of oral bisphosphonates and should not be taken together.
        - Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral bisphosphonates all cause gastrointestinal irritation; caution should be used when administered together.
    - EVISTA
        - Cholestyramine, warfarin, and highly protein-bound drugs all interact with EVISTA.
    - FORTEO
        - Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use teriparatide with caution

- MIACALCIN
  - Concomitant use of MIACALCIN and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium; the dose of lithium may require adjustment.

- Risk Evaluation and Mitigation Strategy (REMS)
  - PROLIA has a REMS program with the goal of mitigating the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions.
    - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe PROLIA.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Bisphosphonates				
ACTONEL (risedronate)	Tablet: 5 mg, 30 mg, 35 mg, 150 mg	• Prevention/ treatment of postmenopausal osteoporosis: 5 mg once daily; 35 mg once a week; or 150 mg once a month • Osteoporosis in men: 35 mg once a week • Prevention/ treatment of glucocorticoid-induced osteoporosis: 5 mg once daily • Paget's disease: 30 mg once daily for 2 months. May repeat times one if failure	Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food or drink of the day other than water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 30 minutes after taking the medication.
ATELVIA (risedronate)	Tablet, delayed release: 35 mg	• 35 mg once weekly	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of ATELVIA and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Tablet should be taken immediately after breakfast. • Swallow while in an upright position with 4 oz of water. • Patients should not lie down for 30 minutes after taking the medication. • Tablet should not be chewed, cut or crushed.
BINOSTO (alendronate)	Tablet, effervescent: 70 mg	• Treatment of postmenopausal osteoporosis: 70 mg once weekly • Osteoporosis in men: 70 mg once weekly	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of BINOSTO and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food, drink or medication of the day other than water. • Dissolve the effervescent tablet in 4 oz room temperature plain water only • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
BONIVA (ibandronate)	Tablet: 150 mg Injectable syringe: 3 mg/3mL	• 150 mg once monthly on the same date each month • 3 mg IV every 3 months	Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration. Injectable should be given IV over 15 to 30 seconds. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of BONIVA and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 60 minutes before the first food, drink or medication of the day other than water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 60 minutes after taking the medication.
FOSAMAX (alendronate)	Tablet: 5 mg, 10 mg, 35 mg, 40 mg, 70 mg Oral solution: 70 mg/75 mL	• Treatment of postmenopausal osteoporosis: 70 mg once weekly or 10 mg once daily • Prevention of postmenopausal osteoporosis: 35 mg once weekly or 5 mg once daily • Osteoporosis in men: 70 mg once weekly or 10 mg once daily • Treatment of glucocorticoid-induced osteoporosis: 5 mg once daily; postmenopausal women not on estrogen: 10 mg once daily • Paget's disease: 40 mg once daily for 6 months. Retreatment may be considered if not effective.	Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of FOSAMAX and should be taken at a different time of the day. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Take at least 30 minutes before the first food, drink or medication of the day other than plain water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Oral solution should be followed by at least 2 oz of water. • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.
FOSAMAX PLUS D (alendronate/ cholecalciferol)	Tablet: 70 mg/2,800 IU, 70 mg/5,600 IU	• Treatment of postmenopausal osteoporosis: 70 mg alendronate/2800 IU vitamin D3 or one 70 mg alendronate/5600 IU vitamin D3 tablet once weekly. • Osteoporosis in men: 70 mg alendronate/2800 IU vitamin D3 or one 70 mg alendronate/5600 IU vitamin D3 tablet once weekly.	Supplemental calcium should be given if dietary intake is inadequate. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of FOSAMAX PLUS D and should be taken at a different time of the day.	• Take at least 30 minutes before the first food, drink or medication of the day other than plain water. • Swallow while in an upright position and with a full glass of plain water (6 to 8 oz). • Patients should not lie down for 30 minutes after taking the medication and until after their first food of the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
RECLAST (zoledronic acid)	Injection: 5 mg/100 mL	• Treatment of postmenopausal osteoporosis: 5 mg IV once yearly. • Prevention of postmenopausal osteoporosis: 5 mg IV once every two years. • Osteoporosis in men: 5 mg IV once yearly. • Prevention/ treatment of glucocorticoid-induced osteoporosis: 5 mg IV once yearly. • Paget's disease: 5 mg IV once. May retreat if relapse.	Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient.	• Patient should be appropriately hydrated. • Give 10 mL normal saline flush after injection. • Acetaminophen may be given after administration to decrease acute phase reactions. • Infusion should be given over no less than 15 minutes. • Allow refrigerated solution to come to room temperature prior to injection.
Calcitonin				
MIACALCIN (calcitonin-salmon synthetic)	Nasal solution: 3.7 mL (30 day supply) Injection: 200 IU/mL in 2 mL vials	• Treatment of postmenopausal osteoporosis: one spray (200 IU) intranasally once daily, alternating nostrils daily. Or 100 IU SQ or IM once daily. • Paget's Disease: 100 IU (0.5 mL) SQ or IM once daily • Hypercalcemia: 4 IU/kg SQ or IM* every 12 hours. If no response after 1 to 2 days, can increase to 8 IU/kg every 12 hours. If no response after 2 days, increase to 8 IU/kg every 6 hours.	Store unopened bottle in refrigerator. Once opened, store at room temperature. Discard opened bottle after 35 days. If the volume of the injection exceeds 2 mL, IM injection is preferable and multiple sites of injection should be used. Store injection in refrigerator.	Nasal spray: • Before the first dose, allow bottle to reach room temperature. • Before the first dose, the bottle must be primed. • Depress the side arms toward the bottle 5 times to prime it. • Nasal spray does not need to be primed before each daily dose.
Estrogen Agonist-Antagonist				
EVISTA (raloxifene)	Tablet: 60 mg	• All indications: 60 mg once daily	Adequate calcium and vitamin D intake should be assured in patients with osteoporosis.	• Can take with or without meals.
Parathyroid Hormone Analogs				
FORTEO (teriparatide)	Injection: 28 doses of 20 mcg in a prefilled injectable pen	• All indications: 20 mcg SQ once daily	The injection pen should be refrigerated at all times.	• Inject into the thigh or abdominal wall. • Patients should be able to sit or lie down if orthostatic hypotension occurs.
TYMLOS (abaloparatide)	Injection: 28 doses of 80 mcg in a	• 80 mcg SQ once daily	The injection pen should be refrigerated before first use, and can be stored at room	• Inject into the periumbilical region of the abdomen at

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	prefilled injectable pen		temperature after first use up to 30 days.	approximately the same time every day. • The first several doses should be administered where the patient can sit or lie down if necessary, in case symptoms of orthostatic hypotension occur.
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors				
PROLIA (denosumab)	Injection: 1 mL of 60 mg/mL prefilled syringe;	• All indications: 60 mg SQ every 6 months	Administered by a healthcare professional. Hypocalcemia must be corrected prior to the administration of PROLIA. All patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily. Store in the refrigerator. Discard 14 days after removal from refrigerator.	• Administer in the upper arm, the upper thigh, or the abdomen. • People sensitive to latex should not handle the grey needle cap. • Warm to room temperature prior to injecting.

IU=international units; IV=intravenously; SQ=subcutaneously; IM=intramuscularly; oz=ounces

CONCLUSION

- To prevent and/or treat osteoporosis in postmenopausal women and men, national guidelines recommend adequate calcium and vitamin D intake, weight bearing exercise, cessation of smoking, and limiting alcohol intake (Adler et al, 2016; Buckley et al, 2017; Camacho et al, 2016; Committee on Practice Bulletins – Gynecology, 2012; Cosman et al, 2014; Florence et al, 2013; Qaseem et al, 2017; Watts et al, 2012).
- Within the various treatment guidelines for osteoporosis in men and women there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (Adler et al, 2016; Camacho et al, 2016; Cosman et al, 2014; North American Menopause Society 2010; Qaseem et al, 2017; Watts et al, 2012).
    - Bisphosphonates are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another.
    - Other antiresorptive drugs approved for osteoporosis include calcitonin, raloxifene and denosumab. These are not considered first-line therapies due to adverse events, less evidence of efficacy, and route of administration.
- Data for hip, vertebral, and nonvertebral fractures is most robust for alendronate, risedronate and zoledronic acid. Ibandronate has data to support reduced vertebral fractures (Guanabens et al, 2013; Harris et al, 2009; Miller et al, 2008[a]).
- Because medication adherence may pose challenges for osteoporosis prevention and treatment, choice of a bisphosphonate should be based on ease of administration for the patient. For instance, ATELVIA (risedronate delayed release) and FOSAMAX (alendronate) are administered once weekly while ACTONEL (risedronate) and ibandronate can be administered once a month. Additionally, zoledronic acid is an intravenous infusion given once a year for treatment or every other year for prevention. ATELVIA (risedronate delayed release) can be taken immediately after eating or drinking. An observational study found 2-year persistence and compliance were higher in women initiating osteoporosis with injectable therapies compared to oral therapies (Durden et al, 2017).
- The receptor activator of nuclear factor K-B ligand inhibitor, PROLIA (denosumab), has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. National guidelines recommend it as an alternative to the bisphosphonates (Committee on Practice Bulletins – Gynecology, 2012; Florence et al, 2013). However, the American Association of Clinical Endocrinologists (AACE) recommends PROLIA as an optional first-line treatment in post-menopausal women (Camacho et al, 2016). Monitoring for infection is required with this agent.
- FORTEO (teriparatide) is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (Camacho et al, 2016; Committee on Practice Bulletins – Gynecology, 2012; Watts

et al, 2012). TYMLOS (abaloparatide) is the most recent parathyroid hormone analog approved by the FDA, and is not included in current osteoporosis guidelines. Both FORTEO (teriparatide) and TYMLOS (abaloparatide) are administered via daily subcutaneous injection, and treatment duration should not exceed two years. Osteosarcoma is a risk and there are insufficient data to demonstrate reduction in hip fractures with these agents.

- Raloxifene has data for vertebral fracture reduction and is only approved for women. It may be an appropriate initial therapy for patients requiring drugs with spine-specific efficacy who are unable to tolerate bisphosphonates (Camacho et al, 2016). Raloxifene is also a breast cancer risk-reduction agent, which is recommended for asymptomatic women ≥35 years of age who are at risk for breast cancer. Depending on individual patient characteristics, raloxifene may be a preferred option (Moyer et al, 2013). There is an increased risk of thromboembolism and stroke with this agent.
- MIACALCIN (calcitonin-salmon) lacks efficacy data for fracture reduction in osteoporosis treatment.
- For the treatment of Paget's disease, risedronate, alendronate, MIACALCIN (calcitonin-salmon injectable), and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, FORTEO (teriparatide), alendronate, and zoledronic acid are all indicated. Selection of an agent should be based on patients' preference of administration. FORTEO (teriparatide) should be reserved for higher doses of steroids and longer lengths of treatment per the national guidelines (Buckley et al, 2017).
- The various other indications for the agents in this class have clinical trial data supporting their use.

REFERENCES

- ACTONEL prescribing information. Warner Chilcott. Rockaway, NJ. April 2015.
- Adler RA, Fuleihan GE, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a task force of the American society for bone and mineral research. J Bone & Miner Res. 2016;31(1):16-35.
- Anabolic therapies for osteoporosis in postmenopausal women: effectiveness and value (evidence report). Prepared by the California Technology Assessment Forum (CTAF). 2017. https://icer-review.org/material/osteo-evidence-report/?utm_source=Osteo+Evidence+Report&utm_campaign=Osteo+evidence+report&utm_medium=email. Accessed June 21, 2017.
- Anastaskilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res. 2009;41:721-729.
- ATELVIA prescribing information. Warner Chilcott. Rockaway, NJ. April 2015.
- Bachmann G, Kriegman A, Goncalves J, et al. Effect of zoledronic acid compared to raloxifene on bone turnover markers in postmenopausal women with low bone density. Menopause. 2011;18(8):851-856.
- Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355(2):125-137.
- BINOSTO prescribing information. Mission Pharmacal Company. San Antonio, TX. December 2016.
- Black DM, Cummings SR, Karpf DB, et al. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348:1535-41.
- Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002 Oct;87(10):4528-35.
- Bone HG, Chapuriat R, Brandi ML, et al. The effect of 3 or 6 years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clin Endocrin Metab. 2013;98(11):4483-4492.
- BONIVA prescribing information. Genentech USA, Inc. South San Francisco, CA. December 2016.
- Bonnick S, Saag KG, Kiel DP, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate vs risedronate over two years. J Clin Endocrinol Metab. 2006;91:2631-2637.
- Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009;24:153-161.
- Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017 Jun 6. doi:10.1002/art.40137 [Epub ahead of print].
- Cadarette SM, Katz JN, Brookhart A, et al. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. Ann Intern Med. 2008;148:637-646.
- Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016. Endocr Pract. 2016;22(Suppl 4):1-42.
- Chen LX, Zhou ZR, Li YL, et al. Comparison of Bone Mineral Density in Lumbar Spine and Fracture Rate among Eight Drugs in Treatments of Osteoporosis in Men: A Network Meta-Analysis. PLoS ONE. 2015;10(5):e0128032.
- Chestnut CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. Am J Med. 2000;109(4):267-276.
- Committee on Practice Bulletins – Gynecology. Practice bulletin. Clinical guidelines for Obstetricians and Gynecologists. Osteoporosis. Obstetrics & Gynecology. 2012;120(3):718-734.
- Cosman F, Eriksen EF, Recknor C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. J Bone Miner Res. 2011;26(3):503-511.
- Cosman F, Lindsay R, LeBoff MS for the National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation: Washington, DC. April 1, 2014. Available at: https://my.nof.org/bone-soruce/education/clinicians-guide-to-the-prevention-and-treatment-of-osteoporosis. Accessed July 17, 2017.
- Cosman F, Miller PD, Williams GC, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. Mayo Clin Proc. 2017;92(2):200-210.
- Cosman R, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresportive agent. J Clin Endrocinol Metab. 2009;94:3772-3780.
- Crandall CJ, Newberry SJ, Gellad WG, et al. Treatment to prevent fractures in men and women with low bone density or osteoporosis: update of a 2007 report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No.

HHSA-290-2007-10062-I.) Rockville, MD: Agency for Healthcare Research and Quality; March 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed June 28, 2017.
- Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev. 2002[a];23(4):524-528.
- Cranney A, Tugwell P, Zytaruk N, et al; Osteoporosis Methodology Group and Osteoporosis Research Advisory Group. Meta-analysis of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. Endoc Rev. 2002[b];23(4):540-551.
- Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. JAMA. 1999;281(23):2189-2197.
- Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756-765.
- Downs RW JR, Bell NH, Ettinger MP, et al. Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. J Clin Endocrinol Metab. 2000;85(5):1783-1788.
- Drugs@FDA. FDA Approved Drug Products. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed July 14, 2017.
- Durden E, Pinto L, Lopez-Gonzalez L, Juneau P, Barron R. Two-year persistence and compliance with osteoporosis therapies among postmenopausal women in a commercially insured population in the United States. Arch Osteoporos. 2017;12(1):22.
- Eastell R, Nickelsen T, Marin F, et al. Sequential treatment of severe postmenopausal osteoporosis after teriparatide: final results of the randomized, controlled, European Study of Forteo (EUROFORS). J Bone Miner Res. 2009;24:726-736.
- Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromastase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008;26(30):4875-4882.
- Ensrud K, Genazzani AR, Geiger MJ, et al. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. Am J Cardiol. 2006;97:520-527.
- Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a three-year randomized clinical trial. JAMA. 1999;282(7):637-624.
- EVISTA prescribing information. Lilly USA, LLC. Indianapolis, IN. December 2016.
- Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med. 2003;349(13):1216-1226.
- Finkelstein JS, Leder BZ, Burnett SM, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. J Clin Endocrinol Metab. 2006;91(8):2882-287.
- Florence R, Allen S, Benedict L, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Osteoporosis. Updated July 2013. Available at: https://www.icsi.org/_asset/vnw0c3/Osteo.pdf. Accessed June 28, 2017.
- Food and Drug Administration (FDA). Approved Risk Evaluation and Mitigation Strategies (REMS). Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed July 14, 2017.
- FORTEO prescribing information. Lilly USA, LLC. Indianapolis, IN. October 2016.
- FOSAMAX PLUS D prescribing information. Merck and Co., Inc. Whitehouse Stations, NJ. March 2016.
- FOSAMAX prescribing information. Merck and Co., Inc. Whitehouse Station, NJ. March 2016.
- Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. J Bone Miner Res. 2013;28(6):1355-1368.
- Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015 Aug 1;386(9992):433-43. doi: 10.1016/S0140-6736(15)60995-3.
- Guanabens N, Monegal A, Cerda D, et al. Randomized Trial Comparing Monthly Ibandronate and Weekly Alendronate for Osteoporosis in Patients With Primary Biliary Cirrhosis. Hepatology. 2013;58(6):2070-208.
- Harris ST, Reginster JY, Harley C, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the evaluation of ibandronate efficacy (VIBE) database fracture study. Bone. 2009;44:758-765.
- Hwang JS, Tu ST, Yang TS, et al. Teriparatide vs calcitonin in the treatment of Asian postmenopausal women with established osteoporosis. Osteoporos Int. 2006;17:373-378.
- Johnston Jr CC, Bjarnason NH, Cohen FJ, et al. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women. Arch Intern Med. 2000;160:3444-3450.
- Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. Osteoporos Int. 2005;16:475-482.
- Kanis JA, Horn DB, Scott RDM, Strong JA. Treatment of Paget's disease of bone with synthetic salmon calcitonin. Br Med J. 1974;3:727-731.
- Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16:510-516.
- Kung AWC, Chao HT, Huang KE, et al. Efficacy and safety of raloxifene 60 mg/day in postmenopausal Asian women. J Clin Endocrinol Metab. 2003;88:3130-136.
- Langdahl BL, Marin F, Shane E, et al. Teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. Osteoporos Int. 2009;20(12):2095-2104.
- Langdahl BL, Teglbjaerg CS, Ho P, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab. 2015;100:1335–1342.
- Leder BZ, Tsai JN, Uihlein AV, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA extension study): a randomized controlled trial. J Clin Endocrinol Metab. 2014;99:1694-1700.
- Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res. 2007;22:1832-1841.
- Lin T, Wang C, Cai XZ, et al. Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. Int J Clin Pract. 2012;66(4):399-408.
- Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med. 2004;164:2024-2030.
- Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799-1809.

- Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst. 2004;96(23):1751-1761.
- McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone. 2007;41:122-128.
- McClung MR, Lewiecki M, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354:821-831.
- McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med. 2005;165:1762-1768.
- MIACALCIN injection prescribing information. Mylan Institutional LLC. Rockford, IL. January 2016.
- MIACALCIN nasal spray prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. March 2014.
- Micromedex® 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed July 14, 2017.
- Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone. 2008[b];43:222-229.
- Miller PD, Epstein S, Sedarati F, Reginster JY. Once-monthly oral ibandronate compared to weekly oral alendronate in postmenopausal osteoporosis: results from the heat-to-head MOTION study. Curr Med Res Opin. 2008[a];24(1):207-213.
- Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722-33.
- Minne H, Audrah M, Simones ME, et al. Bone density after teriparatide in patients with or without antiresportive treatment: one-year results from the EUROFORS study. Curr Med Res Opin. 2008;24(11):3117-3128.
- Mok CC, Tong KH, To CH, et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. Osteoporos Int. 2008;19:357-364.
- Moyer VA, US Preventive Services Task Force (USPSTF). Medications to decrease the risk for breast cancer in women: recommendations from the US Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159(10):698-708.
- Nayak S, Greenspan SL. Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2017 Mar;65(3):490-495.
- Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-1441.
- North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. 2010;17(1):25-54.
- Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresportive treatment. J Bone Miner Res. 2008;23(10):1591-1600
- Okada Y, Nawata M, Nakayamada S, et al. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol. 2008;35:2249-2254.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 14, 2017.
- Orwoll ES, Miller PD, Adachi JD, et al. Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg vs a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res. 2010;25(10):2239-2350.
- Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis (abstract). J Bone Miner Res. 2003;18(1):9-17.
- PROLIA prescribing information. Amgen, Inc. Thousand Oaks, CA. May 2017.
- Qaseem A, Forciea MA, McLean RM, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Ann Intern Med. 2017;166(11):818-839.
- Recker RR, Kendler D, Recknor CP, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. Bone. 2007;40:843-851.
- Recknor C, Czerwinski E, Bone HG, et al. Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. Obstet Gynecol. 2013;121(6):1291-1299.
- RECLAST prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. July 2017.
- Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicenter, double-blind, double-dummy, randomized controlled trial. Lancet. 2009;373:1253-1263.
- Reid DM, Hosking D, Kendler D, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmenopausal women with osteoporosis: 24-month results from FACTS-international. Int J Clin Pract. 2008;62(4):575-584.
- Reid DM, Hosking D, Kendler D, et al. Alendronic acid produces greater effects than risedronic acid on bone density and turnover in postmenopausal women with osteoporosis: results of FACTS-International. Clin Drug Invest. 2006;26(2):63-74.
- Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl JMed. 2005;353(9):898-908.
- Ringe JD, Farahman P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int. 2009;29:311-315.
- Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357(20):2028-2039.
- Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis. Thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009;60(11):3346-3355.
- Sarioglu M, Tuzum C, Unlu Z, et al. Comparison of the effects of alendronate and risedronate on bone mineral density and bone turnover markers in postmenopausal osteoporosis. Rheumatol Int. 2006;26:195-200.
- Sawka AM, Papaioannou A, Adachi JD, et al. Does alendronate reduce the risk of fracture in men? A meta-analysis incorporating prior knowledge of anti-fracture efficacy in women. BMC Musculoskelet Disord. 2005;6:39.
- Silverman SL, Watts NB, Delmas PD, et al. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. Osteoporos Int. 2007;18:25-34.
- Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after eight years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005;20(9):1514-1524.

- Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012;379:39-46.
- Tadrous M, Wong L, Mamdani MM, et al. Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis. Osteoporos Int. 2014;25:1225-1235.
- Tanaka M, Itoh K, Matsushita K, et al. Effects of raloxifene on bone mineral metabolism in postmenopausal Japanese women on hemodialysis. Ther Apher Dial. 2011 Jun;15(Suppl 1):S62-S6.
- Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet. 2013;382: 50–56.
- Tymlos prescribing information. Radius Health, Inc. Waltham, MA. April 2017.
- Vogel VG, Constantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727-2741.
- Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer. Cancer Prev Res (Phila). 2010;3(6):696-706.
- Wang YK, Qin SQ, Ma T, et al. Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96(21):e6970.
- Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: An endocrine society clinical practice guideline. J Clin Endocrin Metab. 2012; 97(6):1802–1822.
- Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocr Pract. 2010;16(Suppl 3):S1-S37.
- Woodhouse NJY, Chalmers AH, Wells IP, et al. Paget's disease. Radiological changes occurring in untreated patients and those on therapy with salmon calcitonin during two years' observation. Br J Radiol. 1977;50(598):699-705.
- World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. Geneva, World Health Organization, 1994 (WHO technical report series, No. 843).
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 2002;288(3):321-333.
- Yang XC, Deng ZH, Wen T, et al. Network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. Cell Physiol Biochem. 2016;40(3-4):781-795.

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Therapeutic Class Overview
Anti-migraine Agents (triptans)

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into two major subtypes: without aura (the most common subtype and is associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (Cutrer et al, 2013; Snow et al, 2002; IHS, 2013; IHS, 2016).
- The migraine one-year prevalence rate in Americans is approximately 13% (18% of women and 6 to 7% of men) (Bajwa et al, 2015; Lipton et al, 2001).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend that the primary outcome for trials measuring acute treatment of migraines is the proportion of patients who are pain-free at two hours (FDA Industry Guidance [migraine], 2014; Tfelt-Hansen et al, 2012).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (Clinical Pharmacology, 2016). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2015).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan is also approved for cluster headaches. Those agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating superiority of any triptan, making it difficult to recommend the use of one over another (Bajwa et al, 2015). Some treatment guidelines do not differentiate among various formulations (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012; Erratum in Subcommittee of the American Academy of Neurology [AAN] and the American Headache Society [AHS], 2013; Snow et al, 2002). Additional key therapies for the treatment of migraines include nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (DHE nasal spray or inhaler), and opioid medications; however, some medications are not recommended for regular use (Marmura et al, 2015; Silberstein et al, 2012; Erratum in Subcommittee of the AAN and the AHS, 2013). For the treatment of cluster headaches, the 2016 AHS recommends subcutaneous sumatriptan and zolmitriptan nasal spray (Robbins et al, 2016). In pediatric patients, the Child Neurological Society recommends ibuprofen, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004).
- Currently available triptans include oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), transdermal patch (sumatriptan), and subcutaneous injection (sumatriptan) formulations (DRUGS@FDA, 2017). Branded products are outlined in Table 1.
- According to DRUGS@FDA, the marketing status of ALSUMA is discontinued; therefore, this product has been removed from the therapeutic class overview (DRUGS@FDA, 2017). ZECUITY has been voluntarily withdrawn from the market due to post-marketing reports of application site reactions, and it is not clear when and if ZECUITY will re-enter the market (FDA Safety Alert, 2016).
- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMERGE (naratriptan hydrochloride tablet)	various	02/10/1998	✔
AXERT (almotriptan malate tablet)	various	05/07/2001	✔
FROVA (frovatriptan succinate tablet)	various	11/08/2001	✔
IMITREX (sumatriptan tablet, nasal spray, injection)	various	12/28/1992	✔
IMITREX STATDOSE (sumatriptan cartridges for injection)	various	12/23/1996	✔
MAXALT (rizatriptan benzoate tablet)	various	06/29/1998	✔
MAXALT MLT (rizatriptan benzoate orally disintegrating tablet)	various	06/29/1998	✔
ONZETRA XSAIL (sumatriptan nasal powder)	Merck & Co., Inc.	01/27/2016	-
RELPAX (eletriptan hydrobromide tablet)	Pfizer	12/26/2002	-
SUMAVEL DOSEPRO (sumatriptan needle-free injection)	Zogenix, Inc.	07/15/2009	-
TREXIMET (sumatriptan/naproxen sodium tablet)	GlaxoSmithKline	04/15/2008	-
ZECUITY* (sumatriptan iontophoretic transdermal patch)	Nupathe Inc.	01/17/2013	-
ZEMBRACE SYMTOUCH (sumatriptan injection)	Nupathe Inc.	01/28/2016	-
ZOMIG (zolmitriptan nasal spray, tablet)	various	09/30/2003	✔ (tablets only)
ZOMIG-ZMT (zolmitriptan orally disintegrating tablet)	various	02/13/2001	✔

*Sales, marketing, and distribution have voluntarily been suspended by the manufacturer due to post-marketing reports of application site reactions.

(DRUGS@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents														Combo
	AMERGE (naratriptan tablet)	AXERT (almotriptan tablet)	FROVA (frovatriptan tablet)	IMITREX (sumatriptan tablets, nasal spray, injection)	IMITREX STATDOSE (sumatriptan cartridges for injection)	MAXALT (rizatriptan tablet)	MAXALT MLT (rizatriptan ODT)	ONZETRA XSAIL (sumatriptan nasal powder)	RELPAX (eletriptan tablet)	SUMAVEL DOSEPRO (sumatriptan needle-free injection)	ZECUITY (sumatriptan iontophoretic transdermal patch)	ZEMBRACE SYMTOUCH (sumatriptan injection)	ZOMIG (zolmitriptan nasal spray, tablet)	ZOMIG ZMT (zolmitriptan ODT)	TREXIMET (sumatriptan/naproxen tablet)
Adult															
Acute treatment of migraine with or without aura	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔ ‡	✔	✔
Acute treatment of cluster headache				✔ *†	✔					✔					
Pediatric															
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔								
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ four hours when untreated (aged ≥ 12 years)		✔ §													
Acute treatment of migraine with or without aura (aged ≥ 12 years)													✔ †‡		✔

Abbrv: ODT = orally disintegrating tablet
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
Class Limitations of Use: All agents in class are not intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established.

(Prescribing information: AMERGE, 2016; AXERT, 2014; FROVA, 2013; IMITREX injection, 2015; IMITREX nasal spray, 2013; IMITREX tablets, 2013; MAXALT, 2015; MAXALT MLT, 2015; ONZETRA XSAIL, 2016; RELPAX, 2013; SUMAVEL DOSEPRO, 2016; TREXIMET, 2016; ZECUITY, 2015; ZEMBRACE SYMTOUCH, 2017; ZOMIG nasal spray, 2015; ZOMIG tablets, 2012; ZOMIG ZMT, 2012)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at two hours and sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (Bird et al, 2014; Brandes et al, 2007; Cady et al, 2015; Derry et al, 2012 [a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Goldstein et al, 2012; Law et al, 2016; Oldman et al, 2002; Pascual et al, 2007; Poolsup et al, 2005; Prescribing information: IMITREX, 2015; ZEMBRACE SYMTOUCH, 2017; Richer et al, 2016).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of one over another, suggesting that individual variations in the response to different triptans exist. 5-HT_1 receptor agonists have been evaluated in numerous meta-analyses and comparative trials with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All 5-HT_1 receptor agonists are effective at treating migraines and are well-tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (Derry et al, 2012[a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Oldman et al, 2002; Pascual et al, 2007):
  - Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-free and headache relief at two hours post-dose for oral agents (Oldman et al, 2002); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (Ferrari et al, 2002; Pascual et al, 2007). Naratriptan 2.5 mg has lower efficacy rates of pain-free and headache relief at two hours (Pascual et al, 2007) while eletriptan has a lower rate of recurrence (Ferrari et al, 2002).
  - Subcutaneous sumatriptan is the most effective for migraine treatment but is associated with more adverse events (AEs) relative to the other 5-HT_1 receptor agonist formulations (Oldman et al, 2002; Derry et al, 2012[c]).
  - Frovatriptan has the least number of head-to-head trials with active comparators. A recent pooled analysis of three studies showed similar efficacy at two hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group (P<0.001) (Cortelli et al, 2011).
  - Sumatriptan/naproxen fixed dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at two hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (Brandes et al, 2007).
  - Sumatriptan iontophoretic TDS had significantly higher proportions of patients with pain-free and headache relief responses compared to placebo in a single migraine headache study, and sumatriptan iontophoretic TDS was well-tolerated with most AEs related to application site reactions (Goldstein et al, 2012).
  - Most 5-HT_1 receptor agonists are well-tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (Ferrari et al, 2002).
- Recent evidence is summarized below:
  - The newest intranasal sumatriptan formulation, ONZETRA XSAIL, was evaluated in two double-blind (DB), randomized trials in 498 patients with moderate to severe migraines through the TARGET and COMPASS studies. The TARGET study (n=230) resulted in significantly more patients who experienced headache relief at two hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs. 45%, respectively; P=0.002). At 30 minutes post-dose, significant difference in relief was maintained between treatment groups (42% vs. 27%; P=0.03) (Cady et al, 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n=275; 1,531 migraines assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores (P<0.001). At two hours, the rates of pain relief (freedom) were comparable (Tepper et al, 2015).
  - Data to support the approval of ZEMBRACE SYMTOUCH were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in three controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (Prescribing Information: ZEMBRACE SYMTOUCH, 2017; IMITREX, 2015).

- A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first two hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-free after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs. sumatriptan 25 mg), rizatriptan 10 mg (vs. sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs. sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence AEs were found (Derry et al, 2014).
- A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at two hours (range 66 to 68%) with no significant difference in safety (Bird et al, 2014).
- The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. The DB, four-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after two hours of administration (29.7% vs. 16.6%, respectively; P<0.001). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% more of patients) (Winner et al, 2016).
- In pediatric patients, one Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing pain freedom in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be with higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (Richer et al, 2016).

SAFETY SUMMARY

- The manufacturer of sumatriptan iontophoretic TDS has received post-marketing reports of application site reactions described as burns and scars in patients treated with sumatriptan iontophoretic TDS. Distribution of sumatriptan iontophoretic TDS has been voluntarily suspended. Patients are recommended to discontinue sumatriptan iontophoretic TDS and discuss alternative treatment options with their physicians.
- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT_1 receptor agonist. Additional contraindications include:
  - Eletriptan, naratriptan, sumatriptan, and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within two weeks) use of an MAO-A inhibitor.
  - Allergic contact dermatitis to sumatriptan iontophoretic TDS.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in asthma, rhinitis, and in those patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID-use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.
- The following warnings and precautions are associated with medications in class:
  - Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac

events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vaso-spasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome (with the exception of sumatriptan iontophoretic TDS).
  - Almotriptan and eletriptan have additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides. Eletriptan has had reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures reported following administration. Sumatriptan iontophoretic TDS have additional warnings of allergic contact dermatitis, a risk of injury during magnetic resonance imaging procedure, and drug should not be applied near or over electrically-active implantable or body-worn medical devices. Sumatriptan/naproxen also has a warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema may worsen heart failure or cause hyperkalemia and renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); the potential to mask inflammation and fever; and elevated liver enzymes have been reported with use.
  - Zolmitriptan ODTs contain phenylalanine, in which the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - Generally, the most common AEs associated with 5-HT_1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT_1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Oral agents			
AMERGE (naratriptan)	Tablet: 1 mg 2.5 mg	Adult: 1 mg or 2.5 mg orally as a single dose; may repeat administration in four hours. Max daily dose: 5 mg.	Safety of treating >4 migraines in one month has not been established.
AXERT (almotriptan)	Tablet: 6.25 mg 12.5 mg	Adult and adolescent (≥12 years): 6.25 mg or 12.5 mg orally as a single dose; may repeat administration in two hours. Max daily dose for adults: 25 mg.	Safety of treating >4 migraines in one month has not been established. In adults, 12.5 mg dose is more effective.
FROVA (frovatriptan)	Tablet: 2.5 mg	Adult: 2.5 mg orally as a single dose; may repeat administration in two hours. Max daily dose: 7.5 mg.	Safety of treating >4 migraines in one month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
IMITREX (sumatriptan)	Tablet: 25 mg 50 mg 100 mg	Adult: 25, 50, or 100 mg orally as a single dose; may repeat administration in two hours. Max daily dose: 200 mg.	Safety of treating >4 migraines in one month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose.
MAXALT, MAXALT MLT (rizatriptan)	Orally disintegrating tablet; Tablet: 5 mg 10 mg	Adult: 5 mg or 10 mg orally as a single dose. Max daily dose: 30 mg. Pediatric (≥6 years): Weight based dosing of 5 mg for <40 kg and 10 mg for ≥40 kg. May repeat administration in two hours in adults and 24 hours in pediatric patients. Dose adjustments are needed for patients taking propranolol concomitantly.	Safety of treating >4 migraines/month in adults or children, and >1 dose within 24 hours in patients six to 12 years of age have not been established.
RELPAX (eletriptan)	Tablet: 20 mg 40 mg	Adult: 20 or 40 mg orally as a single dose; may repeat administration in two hours. Max daily dose: 80 mg. Max single dose: 40 mg.	Safety of treating >3 migraines in one month has not been established.
TREXIMET (sumatriptan/ naproxen)	Tablet: 10/60 mg 85/500 mg	Adult and adolescent (≥12 years): one tablet (85/500 mg for adults and 10/60 mg for adolescents) orally as a single dose. Max daily dose: two tablets in 24 hours, taken at least two hours apart for adults and one tablet in a 24 hour period for adolescents.	Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of one month has not been established.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Orally disintegrating tablet; Tablet: 2.5 mg 5 mg	Adult: starting dose is 1.25 or 2.5 mg dose; may repeat administration in two hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >3 migraines in one month has not been established.
Intranasal agents			
IMITREX nasal spray (sumatriptan)	Nasal spray: 5 or 20 mg/actuator unit-of-use inhaler	Adult: 5, 10, or 20 mg administered as a single dose intranasally; may repeat administration in two hours. Max daily dose: 40 mg. Max single dose: 20 mg.	Safety of treating >4 migraines in one month has not been established.
ONZETRA XSAIL (sumatriptan)	Nasal powder: two breath-powered delivery systems containing 11 mg sumatriptan per each nosepiece	Adult: 22 mg (two nosepieces) administered using the breath-powered delivery device; may repeat administration in two hours. Max daily dose: two doses (44 mg/4 nosepieces).	Safety of treating >4 migraines in one month has not been established. Breath-powered powder delivery requiring a forceful blow into each nostril.
ZOMIG (zolmitriptan)	Nasal spray: 2.5 or 5 mg/spray single-use nasal spray units	Adult and adolescent (≥12 years): 2.5 mg administered as a single dose intranasally; may repeat administration in two hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >4 migraines in one month has not been established.
Subcutaneous agents			
IMITREX (sumatriptan)	Subcutaneous injection: 6 mg single dose vial	Adult: 6 mg administered subcutaneously; may repeat administration in one hour. Max daily dose: 12 mg. Max single dose: 6 mg,	Administer the needle only to the skin; intramuscular

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	(IM) or intravascular (IV) delivery should be avoided.
IMITREX STATDOSE (sumatriptan)	Subcutaneous injection: 4 and 6 mg single dose, prefilled cartridges for pen use	Adult: 6 mg administered subcutaneously; may repeat administration in one hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided.
SUMAVEL DOSEPRO (sumatriptan)	Subcutaneous injection: 4 mg and 6 mg single dose, prefilled, needle-free, subcutaneous delivery systems	Adult: 6 mg single dose; the 6 mg dose is recommended for cluster headaches. Max daily dose: 12 mg. Max single dose: 6 mg.	Administer dose only to the abdomen or thigh.
ZEMBRACE SYMTOUCH (sumatriptan)	Subcutaneous injection: 3 mg single dose, prefilled autoinjector	Adult: 3 mg injected subcutaneously; each dose should be separated by at least one hour. May administer up to four times per day. Max daily dose: 12 mg. Max single dose: 3 mg.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided. Administer dose to the upper arm or thigh. May be administered at least one hour following a dose of another sumatriptan agent.
Transdermal agents			
ZECUITY* (sumatriptan iontophoretic)	Transdermal patch: 86 mg (delivers 6.5 mg over four hours) iontophoretic TDS supplied in cartons of four systems	Adult: One transdermal patch (delivers 6.5 mg over four hours); if no response to first dose, a second dose may be of no benefit. Max daily dose: two patches. Max single dose: one patch.	Apply to the thigh or upper arm, and applications should not be applied to a previous application site until that site is erythema free for at least three days.

*In June 2016, product was voluntarily and temporarily removed from the market.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
AXERT (almotriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric	Safety and efficacy have not been established in children <12 years of age.	For CrCL ≤30 mL/minute, an initial dose of 6.25 mg and a max dose of 12.5 mg/day are recommended.	Dosage adjustment required for moderate to severe impairment, reduce dose to 6.25 mg and a max dose of 12.5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients who have other CV risk factors.				
RELPAX (eletriptan)	No overall difference in safety or efficacy between elderly and younger patients. BP was increased to a greater extent in elderly patients. Additionally, a statistically significant increased half-life (from 4.4 hours to 5.7 hours) was observed between elderly and younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No significant change in clearance for patients with mild, moderate, or severe impairment; although, BP elevations were observed in this population. No dosage adjustment required.	Use in severe impairment is contraindicated.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Drug would not be expected to cause any adverse effects in breastfed infants, especially if the infant is >2 months; use with caution.
FROVA (frovatriptan)	Mean blood concentrations were 1.5 to 2 times higher in elderly patients versus younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No dosage adjustment is required.	An estimated two-fold increase in AUC is predicted with severe impairment; use with caution. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk. However, because of the long half-life, a shorter-acting drug may be preferred, especially while nursing a newborn or preterm infant; use with caution.
AMERGE (naratriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric	Safety and efficacy have not been established.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment is (CrCL ≤15	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment is	Several studies have suggested women with migraine may be at increased risk of preeclampsia. Post-marketing reports of naratriptan included mainly first trimester exposures. The incidence of major birth defects with

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients who have other CV risk factors.		mL/min) contraindicated.	(Child-Pugh C) contraindicated.	naratriptan was similar to the incidence of the general US population (2.2% vs. 2.2 to 2.9%, respectively). Use with caution. Unknown whether excreted in breast milk; use with caution.
MAXALT, MAXALT MLT (rizatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <6 years of age.	No dosage adjustment is required.	Drug plasma concentrations are 30% greater with moderate impairment. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, SUMAVEL DOSEPRO, ZECUITY, ZEMBRACE SYMTOUCH (sumatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	Not studied.	The maximum single dose oral should not exceed 50 mg. Use in severe impairment is contraindicated.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Withhold breastfeeding for eight hours after a single injection may virtually eliminate infant exposure to the drug; consider in preterm infants. Drug would not be expected to cause any adverse effects in most breastfed infants; use with caution.
TREXIMET (sumatriptan/ naproxen)	Safety and efficacy have not been established. In	Safety and efficacy have not been established in	No renal dosage adjustment required for mild to moderate	Administer one 10/60 mg tablet in a 24 hour period for mild	Pregnancy Category C during the first two trimesters; Pregnancy

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	children <12 years of age.	impairment. Not recommended for severe impairment (CrCL ≤30 mL/min). Renal effects of the drug may hasten progression of renal dysfunction in pre-existing renal disease.	to moderate impairment. Use in severe impairment is contraindicated.	Category X during the third trimester* Both agents are excreted in breast milk. Limited information indicates that levels are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant; use with caution.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established for the nasal spray in children <12 years of age and <18 years of age for oral formulations.	Clearance was reduced by 25% in patients with severe impairment (CrCL ≤25 mL/min); no significant change in clearance was observed in moderate impairment (CrCL 26 to 50 mL/min). No dosage adjustment required.	Dosage adjustment required for moderate to severe impairment, reduce dose to 1.25 mg and a max dose of 5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Abbrv: AAP = American Academy of Pediatrics; AUC = area under the curve; BP = blood pressure; CrCL = creatinine clearance; CV = cardiovascular; ODT = orally disintegrating tablet

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

(American Academy of Pediatrics, 2001; LactMed, 2016)

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2015; Clinical Pharmacology, 2016).
- Currently, there are seven single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and one fixed-dose triptan/nonsteroidal anti-inflammatory combination product (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, tablet, and transdermal patch) and zolmitriptan (nasal spray, orally disintegrating tablet, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (Francis et al, 2010). Almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan are available generically in at least one dosage form or strength (DRUGS@FDA, 2017). As of June 2016, ZECUITY (sumatriptan iontophoretic TDS) has been voluntarily withdrawn from the market due to post-marketing reports of application site reactions. Removal is anticipated to be temporary until ZECUITY is determined to be safe and effective (FDA Safety Alert, 2016).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of ZEMBRACE SYMTOUCH) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as six years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of one triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and –dynamic data, subcutaneous and intranasal formulations generally have a quicker onset of action and subcutaneous formulations generally have a lower NNT but more AEs. Frovatriptan and naratriptan have the longest onset of action which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
- According to the AAN, American College of Physicians-American Society of Internal Medicine, and U.S. Headache Consortium, 5-HT_1 receptor agonists are clinically interchangeable for the treatment of migraines. These guidelines do not provide a recommendation for use of one agent over another. In addition, non-oral formulations provide relief for patients unable to swallow due to symptoms of nausea and vomiting (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012; Erratum in Subcommittee of the AAN and the AHS, 2013; Snow et al, 2002). According to the 2015 AHS evidence assessment, triptans (regardless of formulation) and DHE (nasal spray or inhaler) have been established to be effective treatments for acute migraines in adults. Reaffirming the AAN migraine guidelines, the recommendation remains that clinicians should consider medication efficacy and potential AEs when prescribing acute medications for migraine. Opioid medications are probably effective; however, they are not recommended for regular use (Marmura et al, 2015). For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (Francis et al, 2010; Robbins et al, 2016). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (Robbins et al, 2016). In pediatric patients, older guidelines published by the Child Neurological Society

recommend ibuprofen as first-line therapy for the treatment of migraines, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004).

- All 5-HT_1 receptor agonists are generally effective for the acute treatment of migraine attacks and are well-tolerated with a similar safety profile. Although some 5-HT_1 receptor agonists have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, the clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injection treatments have been associated with the fastest onset of action; therefore, are amenable to quick relief. However, injectable triptans are associated with more AE compared to oral or topical dosage forms. Treatment guidelines do not recommend one agent over another; rather, choice of treatment should be individualized based on patient needs, response, and preference, migraine severity, and tolerability.

REFERENCES

- Amerge prescribing information. GlaxoSmithKline. Research Triangle Park, NC. November 2016.
- American Academy of Pediatrics (AAP) Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108:776-89.
- Axert prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. August 2014.
- Bajwa ZH, Sabahat A. Acute treatment of migraine in adults. [website]. UpToDate. Available at: http://www.uptodate.com/. Accessed April 27, 2017.
- Bird S, Derry S, Moore RA. Zolmitriptan for acute migraine attacks in adults. Cochrane Database Syst Rev. 2014 May 21;5:CD008616.
- Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007;297(13):1443-54.
- Cady RK, McAllister PJ, Spierings EL, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). Headache. 2015 Jan;55(1):88-100.
- Clinical Pharmacology. Elsevier/Gold Standard [database on internet]. 2016. Available at: www.clinicalpharmacology.com. Accessed April 27, 2017.
- Cortelli P, Allais G, Tullo V, et al. Frovatriptan versus other triptans in the acute treatment of migraine: pooled analysis of three double-blind, randomized, cross-over, multicenter, Italian studies. Neurol Sci. 2011;32 Suppl 1:S95-8.
- Cutrer FM, Bajwa ZH, Sabahat A. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. [website]. UpToDate. Available at: http://www.uptodate.com/. Accessed April 27, 2017.
- Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults – overview of Cochrane reviews. Cochrane Database Syst Rev. 2014 May 28;5:CD009108.
- Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012[a];2:CD009663.
- Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012[b];2:CD008615.
- Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012[c];2:CD009665.
- Drugs@FDA. [website]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 27, 2017.
- Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.
- Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002;22(8):633-58.
- FDA Guidance for Industry. Migraine: Developing Drugs for Acute Treatment. October 2014. Available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm419465.pdf. Accessed April 27, 2017.
- FDA Safety Alert. Urgent - Zecuity (sumatriptan iontophoretic transdermal system): Suspension of marketing. Teva Pharmaceuticals. June 10, 2016. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM506332.pdf. Accessed April 27, 2017.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventative pharmacologic treatment of cluster headache. Neurology. 2010;75:463-73.
- Frova prescribing information. Endo Pharmaceuticals Inc. Malvern, PA. October 2013.
- Goldstein J, Smith TR, Pugach N, Griesser J, Sebree T, Pierce M. A sumatriptan iontophoretic transdermal system for the acute treatment of migraine. Headache. 2012;52(9):1402-10.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
- Imitrex nasal spray prescribing information. GlaxoSmithKline. Research Triangle Park, NC. November 2013.
- Imitrex injection prescribing information. GlaxoSmithKline. Research Triangle Park, NC. November 2015.
- Imitrex tablets prescribing information. GlaxoSmithKline. Research Triangle Park, NC. November 2013.
- International Headache Society (IHS). IHS Classification ICHD-II. 2016. Available at: http://ihs-classification.org/en/02_klassifikation/02_teil1/01.01.00_migraine.html. Accessed April 27, 2017.
- LactMed. A ToxNet Database. US National Library of Medicine. Available at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2. Accessed April 27, 2017.

- Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database Syst Rev. 2016 Apr 20;4:CD008541.
- Lewis D, Ashwal S, Hershey A, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63:2215-24.
- Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41(7):646-57.
- Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015:3-20.
- Matchar DB, Young WB, Rosenberg JH, et al. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacological management of acute attacks. US Headache Consortium. 2000. Available at: http://www.aan.com. Accessed April 27, 2017.
- Maxalt and Maxalt-MLT prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. March 2015.
- Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. Pain. 2002;97(3):247-57.
- Onzetra Xsail prescribing information. Avanir Pharmaceuticals Inc. Aliso Viejo, CA. January 2016.
- Pascual J, Mateos V, Roig C, Sanchez-Del-Rio M, Jiménez D. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. Headache. 2007;47(8):1152-68.
- Poolsup N, Leelasangaluk V, Jittangtrong J, et al. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. J Clin Pharm Ther. 2005;30(6):521-32.
- Relpax prescribing information. Pfizer. New York, NY. November 2013.
- Richer L, Billinghurst L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev. 2016 Apr 19;4: CD005220.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016 Jul;56(7):1093-106. doi: 10.1111/head.12866.
- Silberstein SD, Holland S, Freitaq F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012 Apr 24;78(17):1337-45.
- Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62.
- Snow V, Weiss K, Wall EM, Mottur-Pilson C, for the American Academy of Family Physicians and American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002;137(10):840-9.
- Subcommittee of the American Academy of Neurology and the American Headache Society. Correction: Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2013 Feb 26;80(9):871.
- Sumavel DosePro prescribing information. Zogenix, Inc. San Diego, CA. June 2016.
- Tepper SJ, Cady RK, Silberstein S, et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. Headache. 2015 May;55(5):621-35.
- Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia. Jan 2012;32(1):6-38.
- Treximet prescribing information. GlaxoSmithKline. Research Triangle Park, NC. May 2016.
- Winner P, Farkas V, Stillova H, et al. Efficacy and tolerability of zolmitriptan nasal spray for the treatment of acute migraine in adolescents: Results of a randomized, double-blind, multi-center, parallel-group study (TEENZ). Headache. 2016 Jul;56(7):1107-19.
- Zecuity prescribing information. Nupathe Inc. Conshohocken, PA. April 2015.
- Zembrace SymTouch prescribing information. Dr. Reddy's Laboratories Limited. San Diego, CA. March 2017.
- Zomig nasal spray prescribing information. AstraZeneca. Hayward, CA. June 2015.
- Zomig and Zomig-ZMT prescribing information. AstraZeneca. Hayward, CA. September 2012.

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Therapeutic Class Overview
Ophthalmic Antibiotics and Combinations

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with the symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms including Staphylococcus species, Corynebacterium species and Propionibacterium acnes. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (American Academy of Ophthalmology [AAO], 2013).
- Conjunctivitis occurs worldwide and affects all ages, social strata and both genders. This infection rarely causes permanent visual loss or structural damage, and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (AAO, 2013; American Optometric Association [AOA], 2002).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (AAO, 2013; AOA, 2002).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea. Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In addition, broad-spectrum ophthalmic antibiotics are used initially as empiric treatment. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (AAO, 2013).
- Though not Food and Drug Administration (FDA)-approved, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (AAO, 2016; AAO, 2013; AOA, 2004).
- Medispan class: Ophthalmic Antibiotics, Ophthalmic Anti-infective Combinations, and Ophthalmic Sulfonamides.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aminoglycosides	
Gentak (gentamicin) †	✔
Tobrex (tobramycin) †	✔ *
Macrolides	
Azasite (azithromycin)	-
erythromycin	✔
Other	
bacitracin	✔
Bleph-10 (sulfacetamide sodium)	✔
Quinolones	
Besivance (besifloxacin)	-
Ciloxan (ciprofloxacin)	✔ *
levofloxacin	✔
Moxeza, Vigamox (moxifloxacin)	✔ ‖
Ocuflox (ofloxacin)	✔
Zymaxid (gatifloxacin)	✔
Combinations	
bacitracin/neomycin/polymyxin	✔
bacitracin/polymyxin	✔
Neosporin (gramicidin/neomycin/polymyxin)	✔
Polytrim (polymyxin/trimethoprim)	✔

*solution only

†Brand name Bleph-10 is available in solution only; generics are available for solution and ointment. Cetamide brand of sulfacetamide sodium has been discontinued. Genoptic brand of gentamicin sulfate solution has been discontinued; generic is available. AK-tob brand of tobramycin has been discontinued.

‖Three generic versions of Vigamox have become available, manufactured by Apotex, Sandoz, and Lupin.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017; Drug Facts and Comparisons, 2017; Clinical Pharmacology, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aminoglycosides		Macrolides		Other		Quinolones							Combinations			
	gentamicin	tobramycin	Azasite	erythromycin	bacitracin	sulfacetamide	ciprofloxacin	levofloxacin	ofloxacin	Besivance	Moxeza	Vigamox	Zymaxid	bacitracin/neomycin/polymyxin	bacitracin/polymyxin	gramicidin/neomycin/polymyxin	polymyxin/trimethoprim
Treatment of bacterial conjunctivitis.			✔				✔	✔	✔	✔	✔	✔	✔				
Treatment of corneal ulcers.							✔ †		✔								
Treatment of external infections of the eye and its adnexa caused by susceptible bacteria.		✔												✔		✔	
Treatment of superficial ocular infections involving the conjunctiva and/or cornea.				✔	✔										✔		
Prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae* or *C. trachomatis*.				✔ §													
Treatment of ocular bacterial infections including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.	✔																
Treatment of surface ocular infections, including acute bacterial conjunctivitis and blepharoconjunctivitis.																	✔
Treatment of conjunctivitis and other superficial ocular infections.						✔											
Adjunctive treatment with systemic treatment for trachoma.						✔ †											

† solution only

§ The effectiveness of erythromycin in the prevention of ophthalmia caused by penicillinase-producing *N. gonorrhoeae* is not established.

(Prescribing information: AZASITE, 2013; bacitracin, 2013; bacitracin/neomycin/polymyxin, 2016; bacitracin/polymyxin, 2013; BESIVANCE, 2016; BLEPH-10, 2014; CILOXAN solution, 2017; CILOXAN ointment, 2017; erythromycin, 2016; GENTAK, 2015; gentamicin, 2015; levofloxacin, 2017; MOXEZA, 2017; NEOSPORIN, 2016; OCUFLOX, 2016; polymyxin/trimethoprim, 2013; POLYTRIM, 2004; sulfacetamide ointment, 2013; sulfacetamide solution, 2014; TOBREX ointment, 2008; TOBREX solution, 2012; VIGAMOX, 2017; ZYMAXID, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that ophthalmic antibiotics are effective in treating and providing relief of bacterial conjunctivitis in pediatric and adult patients (Abelson et al, 2007; Abelson et al, 2008; Bremond-Gignac, et al, 2014; Cochereau et al, 2007; DeLeon et al, 2012; Gross et al, 1997; Hwang et al, 2003; Karpecki et al, 2009; Kernt et al, 2005; McDonald et al, 2009; Schwab et al, 2003; Sheikh et al, 2012; Silver et al, 2005; Silverstein et al, 2011; Silverstein et al, 2012; Tauber et al, 2011; Tepedino et al, 2009; Williams et al, 2012). Several studies comparing ophthalmic antibiotics such as azithromycin, besifloxacin, levofloxacin, and moxifloxacin to placebo have concluded that these medications resulted in significantly higher clinical resolution rates at days 1 through 5 (Abelson et al, 2008; DeLeon et al, 2012; Hwang et al, 2003; Karpecki et al, 2009; Silverstein et al, 2011; Tauber et al, 2011; Tepedino et al, 2009).
- In a trial, there was no difference in clinical cure rate between treatment with ophthalmic polymyxin B/trimethoprim and ophthalmic moxifloxacin (P=0.59) (Williams et al, 2012). In a 5-day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (P=0.034); however, clinical cure rates were similar between the two treatments (P value not reported) (Schwab 2003).
- Most other studies have shown no significant difference between ophthalmic antibiotic treatments with regard to bacterial eradication, clinical resolution, clinical response, efficacy, microbial eradication, physician's judgment of resolution, severity rating or symptom improvement (Ableson et al, 2007; Cochereau et al, 2007, Gross et al, 1997; McDonald et al, 2009; Sanfilippo et al, 2017; Silver et al, 2005). While no difference was found between ophthalmic formulations of azithromycin and tobramycin with regard to clinical resolution and bacterial eradication, ophthalmic azithromycin produced the same clinical outcome with 65% fewer drops (Abelson et al, 2007). In all studies, most adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events included burning, ocular discomfort, stinging and tearing (Abelson et al 2007; Cochereau et al, 2007; Gross et al, 1997; McDonald et al, 2009; Schwab et al 2003; Silver et al, 2005; Williams et al, 2012).
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of gentamicin, levofloxacin, ofloxacin, and tobramycin solution were efficacious in resolving or curing multiple ocular infections (Gwon, 1992 Sep; Gwon, 1992 Dec; Kanda et al, 2012). No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement, or overall improvement. In one study, ophthalmic ofloxacin was shown to significantly decrease the cumulative summary score on days 3 through 5 in patients with conjunctival hyperemia, eyelid crusting or discharge, and positive bacterial culture when compared to ophthalmic tobramycin (P<0.05); however, by day eleven, there were no significant differences between the two treatments with regard to clinical, microbial and overall improvement rates (Gwon, 1992 Sep). In studies of patients with multiple diagnoses, the most commonly reported adverse events were similar between treatment groups. The most common adverse events included burning, mild discomfort, and stinging on instillation.
- In one study evaluating the treatment of ophthalmia neonatorum, conjunctivitis in newborn babies principally caused by *N. gonorrhoeae*, prophylaxis with ophthalmic erythromycin ointment was found to be most effective prior to the infant's second week of life. The efficacy of ophthalmic erythromycin prophylaxis from days zero to 14 was statistically significant when compared to no prophylaxis; however, the efficacy was not significant from days 15 to 60 (14 vs 9%; P=0.05 and 7 vs 8%; P=0.92, respectively) (Bell et al, 1993). In another study, ophthalmic erythromycin prophylaxis resulted in significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours to 2 weeks of life when compared to no prophylaxis (18.4 vs 22.4%; P=0.03) (Ali et al, 2007).
- In a study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14 and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14 and 21 (P<0.05 for all), and scores in the ophthalmic

neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 (P<0.05) (Notivol et al, 2004).

CLINICAL GUIDELINES

- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (AAO, 2013).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (AAO, 2013).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5 to 7 day course of treatment, if needed (AAO, 2013; AOA, 2002).

SAFETY SUMMARY

- Contraindication to use of these products is hypersensitivity to any component of the product.
- Warnings/precautions include the following: 1) do not wear contact lenses while infected; 2) prolonged use may result in overgrowth of non-susceptible organisms, including fungi; and 3) cutaneous sensitization may occur with products containing neomycin.
- The most frequent adverse effects were burning, stinging, and irritation upon instillation, redness, blurred vision, itching, swelling, tearing, eye pain and photophobia. Non-ocular reactions can occur and include headache, pharyngitis, dizziness, and allergic reactions. Ciloxan (ciprofloxacin) had a reported incidence of 17% for white crystalline precipitates in corneal ulcer studies.
- These agents are minimally absorbed; therefore, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Gentak (gentamicin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: 2 or 3 times a day **Solution**: every 4 hours *Severe infections:* dosage may be increased to as much as every hour.	Safety and efficacy in neonates have not been established.
Tobrex (tobramycin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: *Mild to moderate disease*: 2 or 3 times a day *Severe infections*: every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation. **Solution**: *Mild to moderate disease*: every 4 hours *Severe infections*: hourly until improvement, following which treatment should be reduced prior to discontinuation	Safety and efficacy have not been established in < 2 months of age.
Azasite (azithromycin)	Ophthalmic solution: 1%	Twice daily, 8 to 12 hours apart for the first 2 days, then once daily for the next 5 days	Safety and efficacy have not been established in < 1 year of age
erythromycin	Ophthalmic ointment: 0.5%	**Superficial infections**: Apply directly to the infected structure up	For neonates: The ointment should not be flushed from the eye following instillation

Drug	Available Formulations	Usual Recommended Frequency	Comments
		to 6 times daily, depending on the severity of the infection. **Prophylaxis of neonatal gonococcal or chlamydial conjunctivitis:** apply into each lower conjunctival sac.	
bacitracin	Ophthalmic ointment: 500 units/gram	Apply directly into the conjunctival sac 1 to 3 times daily	No data in pediatric patients
Bleph-10 (sulfacetamide sodium)	Ophthalmic ointment: 10% Ophthalmic solution: 10%	**Ointment**: every 3 to 4 hours and at bedtime for 7 to 10 days **Solution**: every 2 to 3 hours for 7 to 10 days *Trachoma*: every 2 hours; must also use systemic administration	Safety and efficacy have not been established in < 2 months of age.
Besivance (besifloxacin)	Ophthalmic suspension: 0.6%	Three times daily, 4 to 12 hours apart for 7 days	Safety and efficacy have not been established in < 1 year.
Ciloxan (ciprofloxacin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Corneal ulcers**: *Solution*: every 15 minutes for the first 6 hours, every 30 minutes for the remainder of the first day. Second day: every hour Third through 14th day: every 4 hours **Conjunctivitis**: *Ointment*: 3 times daily for first 2 days, then twice daily for the next 5 days *Solution*: every 2 hours while awake for 2 days, then every 4 hours while awake for next 5 days	**Ointment**: Safety and efficacy have not been established in < 2 years of age. **Solution**: Safety and efficacy have been established in all years.
levofloxacin	Ophthalmic solution: 0.5%	Every 2 hours while awake, up to 8 times per day on days 1 and 2. Then every 4 hours while awake, up to 4 times per day for days 3 to 7	Safety and efficacy have not been established in < 1 year of age
Moxeza, Vigamox (moxifloxacin)	Ophthalmic solution: 0.5% (Moxeza - twice daily formulation), 0.5% (Vigamox - 3 times daily formulation)	**Moxeza**: twice daily for 7 days **Vigamox**: 3 times daily for 7 days	**Moxeza**: Safety and efficacy have not been established in < 4 months of age. **Vigamox**: Safety and efficacy have been established in all ages.
Ocuflox (ofloxacin)	Ophthalmic solution: 0.3%	**Conjunctivitis**: every 2 to 4 hours days 1 and 2, then 4 times daily for days 3 through 7 **Corneal ulcers:** *Days 1 and 2*: every 30 minutes, while awake *Days 3 through 7 to 9*: hourly, while awake *Days 7 to 9 through treatment completion*: 4 times daily	Safety and efficacy have not been established in < 1 year of age.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Zymaxid (gatifloxacin)	Ophthalmic solution: 0.5%	Every 2 hours while awake up to 8 times on day 1, then 4 times per day while awake on days 2 through 7	Safety and efficacy have not been established in < 1 year of age.
bacitracin/ neomycin/ polymyxin	Ophthalmic ointment: bacitracin zinc 400 units, neomycin 3.5 mg, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	Safety and efficacy have not been established in pediatric patients
bacitracin/ polymyxin	Ophthalmic ointment: bacitracin zinc 500 units, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	No data in pediatric patients
Neosporin (gramicidin/ neomycin/ polymyxin)	Ophthalmic solution: neomycin sulfate 1.75 mg, polymyxin B sulfate 10,000 units, gramicidin 0.025 mg	Every 4 hours for 7 to 10 days *Severe infections*: may increase to every hour	Safety and efficacy have not been established in pediatric patients.
Polytrim (polymyxin/ trimethoprim)	Ophthalmic solution: polymyxin B sulfate 10,000 units, trimethoprim 1 mg	*Mild to moderate infections*: Every 3 hours (maximum of 6 doses per day) for a period of 7 to 10 days *Pediatric*: Same dosage	Safety and efficacy have not been established in < 2 months of age.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotics are used to treat ophthalmic infections, including blepharitis, conjunctivitis, and keratitis as well as several others. Classes of ophthalmic antibiotics include aminoglycosides, macrolides, quinolones, and other miscellaneous and combination products. For all FDA-approved indications, a generic ophthalmic antibiotic is available.
- In comparative clinical trials, no one ophthalmic antibiotic has been shown to be more effective than another in bacterial eradication, clinical resolution, clinical response, or symptom improvement.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotics are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated.
- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (AAO, 2013).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (AAO, 2013).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed (AAO, 2013; AOA, 2002).

REFERENCES

- Abelson MB, Heller W, Shapira AM, et al. Clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled, double-masked clinical trial. Am J Ophthalmol. 2008;145:959-6.
- Abelson M, Protzko E, Shapiro A, et al. A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. Clin Ophthalmol. 2007;1:177-82.
- Ali Z, Khadije D, Elahe A, et al. Prophylaxis of ophthalmia neonatorum comparison of betadine, erythromycin and no prophylaxis. J Trop Pediatr. 2007 Dec;53(6):388-92.

- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Bacterial keratitis [guideline on the Internet]. San Francisco (CA): American Academy of Ophthalmology; 2013. Available from: http://www.aao.org/preferred-practice-pattern/bacterial-keratitis-ppp--2013. Accessed May 23, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Blepharitis [guideline on the Internet]. San Francisco (CA): American Academy of Ophthalmology; 2013. Available from: http://www.aao.org/preferred-practice-pattern/blepharitis-ppp--2013. Accessed May 23, 2017.
- American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Conjunctivitis [guideline on the Internet]. San Francisco (CA): American Academy of Ophthalmology; 2013. Available from: http://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013. Accessed May 23, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Refractive errors and refractive surgery [guideline on the Internet]. San Francisco (CA): American Academy of Ophthalmology; 2013. Available from: http://www.aao.org/preferred-practice-pattern/refractive-errors--surgery-ppp-2013. Accessed May 23, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Cataract in the adult eye [guideline on the Internet]. San Francisco (CA): American Academy of Ophthalmology; 2016. Available from: https://www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp-in-press. Accessed May 23, 2017.
- American Optometric Association Consensus Panel on Care of the Adult Patient with Cataract. Care of the adult patient with cataract [guideline on the Internet]. St. Louis (MO): American Optometric Association; 2004 Mar. Available from: http://www.aoa.org/documents/optometrists/CPG-8.pdf. Accessed May 23, 2017.
- American Optometric Association. Optometric Clinical Practice Guideline. Care of the patient with conjunctivitis [guideline on the internet]. St. Louis, MO: American Optometric Association; 2002. Reviewed in 2007. Available at: http://www.aoa.org/documents/optometrists/CPG-11.pdf. Accessed May 23, 2017.
- AZASITE prescribing information. Akorn, Inc. Lake Forest, IL. November 2013.
- Bacitracin ophthalmic ointment prescribing information. Perrigo. Minneapolis, MN. August 2013.
- Bacitracin zinc and polymyxin B sulfate ophthalmic ointment prescribing information. Bausch & Lomb, Inc. Tampa, FL. March 2013.
- Bacitracin zinc, neomycin, and polymyxin B sulfate ophthalmic ointment prescribing information. Citron Pharma. East Brunwick, NJ. April 2016.
- Bell TA, Grayston JT, Krohn MA, et al. Randomized trial of silver nitrate, erythromycin, and no eye prophylaxis for the prevention of conjunctivitis among newborns not at risk for gonococcal ophthalmitis. Pediatrics. 1993 Dec;92(6):755-60.
- BESIVANCE ophthalmic suspension prescribing information. Bausch and Lomb Incorporated. Tampa, FL. June 2016.
- BLEPH-10 ophthalmic solution prescribing information. Allergan, Inc. Irvine, CA. May 2014.
- Bremond-Gignac D, Nezzar H, Bianchi PE, et al for the AZI Study Group. Efficacy and safety of azithromycin 1.5% eye drops in paediatric population with purulent bacterial conjunctivitis. Br J Ophthalmol. 2014;98(6):739-745.
- CILOXAN ophthalmic ointment prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. February 2017.
- CILOXAN ophthalmic solution prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. March 2017.
- Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier/Gold Standard; Updated periodically. Available from: http://www.clinicalpharmacology.com. Accessed May 23, 2017.
- Cochereau I, Meddeb-Ouertani A, Khairallah M, et al. Three-day treatment with azithromycin 1.5% eye drops vs seven-day treatment with tobramycin 0.3% for purulent bacterial conjunctivitis: multicentre, randomized and controlled trial in adults and children. Br J Ophthalmol. 2007;91:465-9.
- DeLeon J, Silverstein BE, Allaire C, et al. Besifloxacin ophthalmic suspension 0.6% administered twice daily for three days in the treatment of bacterial conjunctivitis in adults and children. Clin Drug Investig. 2012 May 1;32(5):303-17.
- Drug Facts and Comparisons [database on the Internet]. St. Louis (MO): Wolters Kluwer Health; 2017. Available from http://eanswers.factsandcomparisons.com. Accessed May 23, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 23, 2017.
- Erythromycin ophthalmic ointment prescribing information. Bausch and Lomb Incorporated. Bridgewater, NJ. July 2016.
- GARAMYCIN ophthalmic solution. Perrigo. Minneapolis, MN. October 2013.
- GENTAK ophthalmic ointment prescribing information. PremierPro Rx. Lake Forest, IL. October 2015.
- Gentamicin ophthalmic solution prescribing information. PremierPro Rx. Lake Forest, IL. October 2015.
- Gross RD, Hoffman RO, Lindsay RN. A comparison of ciprofloxacin and tobramycin in bacterial conjunctivitis in children. Clin Pediatr (Phila). 1997;36:435-44.
- Gwon A. Ofloxacin vs tobramycin for the treatment of external ocular infection. Arch Ophthalmol. 1992 Sep;110(9);1234-7.
- Gwon A. Topical ofloxacin compared to gentamicin in the treatment of external ocular infection. Br J Ophthalmol. 1992 Dec;76(12):714-8.
- Hwang DG, Schanzlin DJ, Rotberg MH, et al; Levofloxacin Bacterial Conjunctivitis Place-controlled Study Group. A phase III, placebo controlled clinical trial of 0.5% levofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Br J Ophthalmol. 2003;87:1004-9.
- Kanda Y, Kayama T, Okamoto S, et al. Post-marketing surveillance of levofloxacin 0.5% ophthalmic solution for external ocular infections. Drugs R D. 2012 Dec 1;12(4):177-85.
- Karpecki P, Depaolis M, Hunter JA, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: A multicenter, prospective, randomized, double-masked, vehicle-controlled, five-day efficacy and safety study. Clin Ther. 2009;31:514-26.

- Kernt K, Martinez M, Bertin D, et al; International Tobrex2x group. A clinical comparison of two formulations of tobramycin 0.3% eye drops in the treatment of acute bacterial conjunctivitis. Eur J Ophthalmol. 2005 Sep-Oct;15(5):541-9.
- Levofloxacin ophthalmic solution. Akorn, Inc. Lake Forest, IL. February 2017.
- McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared to moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009 Sep;116(9):1615-23.
- MOXEZA ophthalmic solution prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. February 2017.
- NEOSPORIN ophthalmic ointment prescribing information. Monarch Pharmaceuticals, Inc. Bristol, TN. July 2016.
- Notivol R, Bertin D, Amin D, et al. Comparison of topical tobramycin-dexamethasone with dexamethasone-neomycin-polymyxin and neomycin-polymyxin-gramicidin for control of inflammation after cataract surgery: results of a multicenter; prospective, three-arm, randomized, double-masked, controlled, parallel-group study. Clin Ther. 2004 Aug;26(8):1274-85.
- OCUFLOX ophthalmic solution prescribing information. Allergan, Inc. Irvine, CA. February 2012.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 23, 2017.
- Polymyxin B sulfate/trimethoprim sulfate ophthalmic solution prescribing information. Allergan, Inc. Irvine, CA. November 2013.
- POLYTRIM ophthalmic solution prescribing information. Allergan, Inc. Irvine, CA. August 2004.
- Sanfilippo CM, Allaire CM, Decory HH. Besifloxacin ophthalmic suspension 0.6% compared with gatifloxacin ophthalmic solution 0.3% for the treatment of bacterial conjunctivitis in neonates. Drugs R D. 2017;17(1):167-175.
- Sheikh A, Hurwitz B, van Schayck CP, et al. Antibiotics versus placebo for acute bacterial conjunctivitis (review). Cochrane Database of Systematic Reviews. 2012;9. Article No.: CD001211. DOI:10.1002/14651858.CD001211.pub3.
- Schwab IR, Friedlaender M, McCulley J, et al; Levofloxacin Bacterial Conjunctivitis Active Control Study Group. A phase III clinical trial of 0.5% levofloxacin ophthalmic solution vs 0.3% ofloxacin ophthalmic solution for the treatment of bacterial conjunctivitis. Ophthalmology. 2003 Mar;110(3):457-65.
- Silver LH, Woodside AM, Montgomery DB. Clinical safety of moxifloxacin ophthalmic solution 0.5% (Vigamox®) in pediatric and nonpediatric patients with bacterial conjunctivitis. Surv Ophthalmol. 2005;50:S55-S63.
- Silverstein BE, Allaire C, Bateman KM, et al. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for three days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. Clin Ther. 2011 Jan;33(1):13-26.
- Silverstein BE, Morris TW, Gearinger LS, et al. Besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis patients with Pseudomonas aeruginosa infections. Clin Ophthalmol. 2012;6:1987-96.
- Sulfacetamide sodium ophthalmic ointment prescribing information. Perrigo. Minneapolis, MN. September 2013.
- Sulfacetamide sodium ophthalmic solution prescribing information. Akorn, Inc. Lake Forest, IL. February 2014.
- Tauber S, Cupp G, Garber R, et al. Microbiological efficacy of a new ophthalmic formulation of moxifloxacin dosed twice-daily for bacterial conjunctivitis. Adv Ther. 2011 Jul;28(7):566-74.
- Tepedino ME, Heller WH, Usner DW, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. Curr Med Res Opin. 2009 May;25(5):1159-69.
- TOBREX ophthalmic ointment prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. July 2008.
- TOBREX ophthalmic solution prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. June 2012.
- VIGAMOX ophthalmic solution prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. March 2017.
- Williams L, Malhotra Y, Murante B, et al. A Single-Blinded Randomized Clinical Trial Comparing Polymyxin B-Trimethoprim and Moxifloxacin for Treatment of Acute Conjunctivitis in Children. J Pediatr. 2012;162(4):857-861.
- ZYMAXID ophthalmic solution prescribing information. Allegra, Inc. Irvine, CA. November 2016.

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Therapeutic Class Overview
Attention-Deficit/Hyperactivity Disorder (ADHD) Agents

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2017*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2017a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2017b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2017c*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2017*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2017d*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, nonstimulant medications may be more appropriate for certain children
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2017e*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔

Drug	Generic Availability
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Metadate ER (methylphenidate HCl ER)	✔
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	✔
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Aptensio XR (methylphenidate HCl ER)	-
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Metadate CD (methylphenidate HCl ER)	✔
methylphenidate HCl extended-release	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

Note: Branded generic Dexedrine (dextroamphetamine sulfate) has been discontinued, but some product may still be available.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Adzenys XR-ODT, Dyanavel XR (amphetamine sulfate ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, Metadate CD, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER)
ADHD*		✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.*	✓							✓			✓	✓	
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications						✓			✓				
Narcolepsy**	✓		✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen	✓										✓		

Indication	Evekeo (amphetamine sulfate)	Adzenys XR-ODT, Dyanavel XR (amphetamine sulfate ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, Metadate CD, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER)
of weight reduction based on caloric restriction for patients refractory to alternative therapy (eg, repeated diets, group programs, and other drugs).†													
Moderate to severe BED in adults										✓			

(*Prescribing Information*: *Adderall 2016*, *Adderall XR 2017*, *Adzenys XR-ODT 2017*, *Aptensio XR 2017*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2017, Desoxyn 2017, Dexedrine Spansule 2017*, *Dyanavel XR 2017*, *Evekeo 2016*, *Focalin 2017*, *Focalin XR 2017*, *Intuniv 2016, Kapvay 2016, Mydayis 2017, Metadate CD 2017, Methylin Oral Solution 2016, methylphenidate chewable tablets 2015; methylphenidate ER 2015; ProCentra 2017*, *QuilliChew ER 2017*, *Quillivant XR 2017*, *Ritalin 2017*, *Ritalin LA 2017*, *Strattera 2017*, *Vyvanse 2017, Zenzedi 2017*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, Metadate CD, Metadate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT is approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [LS] mean 14.3 [95% CI, 12.2 to 16.4] vs. 25.3 [9% CI, 23.0 to 27.6], respectively, p < 0.0001).
  - Mydayis, a new mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 unpublished MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (*Mydayis Prescribing Information 2017*) (see results below in Table 3 below).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

  - A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs. placebo. However, the evidence was of low quality.
  - An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
  - A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.

- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and nonstimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs. approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2017e*, *AAP 2011).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs. methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
  - A study (*Li et al 2016*) evaluating the efficacy of treatments for ADHD (atomoxetine, bupropion, clonidine, guanfacine ER, lisdexamfetamine, methylphenidate) in children and adolescents found that lisdexamfetamine had the highest efficacy, while methylphenidate had the lowest incidence of AEs and ranked second in ADHD-RS scores and third in Conners' Parent Rating Scale-Revised (CPRS) scores. Atomoxetine had the lowest rate of all-cause withdrawals, but its efficacy was lower than that of clonidine, guanfacine ER, lisdexamfetamine, and methylphenidate.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs.

placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs. placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.

- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs. placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, open-label extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led cognitive behavioral therapy (CBT), lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2011), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2015) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
  - The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications
    - Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
    - Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.
  - Combination psychotherapy and pharmacotherapy
    - For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
    - Although limited evidence is available, combined treatment is frequently used in clinical practice.
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
- Atomoxetine is contraindicated for use in patients with glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
amphetamine salts ER)					is needed for severe renal impairment. Use in ESRD is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	*ADHD*: Daily to twice daily *Obesity*: 30 min before each meal	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products. The ER tablets must be swallowed whole and never crushed or chewed.
Methylphenidate ER	3 to 8 h	Tablets			
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Methylphenidate ER					
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Metadate CD (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9 hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing. It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2015, Pharmacist's Letter 2016, Krull 2017e*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2011*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills or capsules; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]; and preference of the patient and parent/guardian (*Krull 2017e*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2017*).

- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs. placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

REFERENCES

- Adderall [package insert], Horsham, PA: Teva Select Brands; December 2016.
- Adderall XR [package insert], Lexington, MA: Shire US Inc.; January 2017.
- Adzenys XR-ODT [package insert], Grand Prairie, TX: Neos Therapeutics, Inc.; January 2017.
- Aigner M, Treasure J, Kaye W, Kasper S; WFSBP Task Force On Eating Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. *World J Biol Psychiatry*. 2011;12(6):400-443.
- Aptensio XR [package insert], Coventry, RI: Rhodes Pharmaceuticals, L.P.; January 2017.
- Brownley KA, Berkman ND, Peat CM, et al. Binge-eating disorder in adults: A systematic review and meta-analysis. *Ann Intern Med*. 2016;165(6):409-420.
- Bukstein O. Attention deficit hyperactivity disorder in adults: Epidemiology, pathogenesis, clinical features, course and diagnosis. UpToDate Web site. 2017. http://www.uptodate.com. Updated November 3, 2016. Accessed June 23, 2017.
- Chan E, Fogler JM, Hammerness PG. Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents: A Systematic Review. *JAMA*. 2016;315(18):1997-2008.
- Childress AC, Kollins SH, Cutler AJ, Marraffino A, Sikes CR. Efficacy, safety, and tolerability of an extended-release orally disintegrating methylphenidate tablet in children 6-12 years of age with attention-deficit/hyperactivity disorder in the laboratory classroom setting. *J Child Adolesc Psychopharmacol*. 2017;27(1):66-74.
- Concerta [package insert], Titusville, NJ: Janssen Pharmaceuticals, Inc.; January 2017.
- Cotempla XR-OD [package insert], Grand Prairie, TX: Neos Therapeutics Brands, LCC; June 2017.
- Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904.
- Cunill R, Castells X, Tobias A, Capellà D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoepidemiol Drug Saf*. 2013;22(9):961-969.
- Daytrana [package insert], Miami, FL: Noven Therapeutics, LLC; January 2017.
- Desoxyn [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; May 2017.
- Dexedrine Spansule [package insert], Horsham, PA: Amedra Pharmaceuticals LLC; May 2017.
- Drug scheduling. Drug Enforcement Administration Web site. http://www.dea.gov/druginfo/ds.shtml. Accessed June 23, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed June 23, 2017.
- Drugs for ADHD. *Med Lett Drugs Ther*. 2015;57(1464):37-40.
- Dyanavel XR [package insert], Monmouth Junction: Tris Pharma, Inc.; May 2017.
- Evekeo [dossier], Atlanta, GA: Arbor Pharmaceuticals, LLC; 2015.
- Evekeo [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; September 2016.
- Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed*. 2006;8(4):4.
- Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry*. 2010a;19(4):353-364.
- Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry*. 2010b;71(6):754-763.
- Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med*. 2014;370(9):838-846.
- Focalin [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Focalin XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Gasior M, Hudson J, Quintero J, Ferreira-Cornwell MC, Radewonuk J, McElroy SL. A phase 3, multicenter, open-label, 12-month extension safety and tolerability trial of lisdexamfetamine dimesylate in adults with binge eating disorder. *J Clin Psychopharmacol*. 2017 ;37(3):315-322.
- Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1284-1293.
- Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA.* 2011;306(24):2673-2683.
- Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):153-173.
- Intuniv [package insert], Lexington, MA: Shire US Inc.; July 2016.
- Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evid Rep Technol Assess (Summ).* 1999;(11):i-viii, 1-341.
- Kapvay [package insert], St. Michel, Barbados: Concordia, Pharmaceuticals, Inc.; August 2016.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Clinical features and diagnosis. UpToDate Web site. 2017a. http://www.uptodate.com. Updated June 4, 2017. Accessed June 23, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Epidemiology and pathogenesis. UpToDate Web site. 2017b. http://www.uptodate.com. Updated March 28, 2017. Accessed June 23, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Overview of treatment and prognosis. UpToDate Web site. 2017d. http://www.uptodate.com. Updated June 14, 2017. Accessed June 23, 2017.
- Krull KR. Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications. UpToDate Web site. 2017e. http://www.uptodate.com. Updated June 1, 2016. Accessed June 23, 2017.

- Krull KR. Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents. UpToDate Web site. 2017c. http://www.uptodate.com. Updated February 23, 2017. Accessed June 23, 2017.
- Li Y, Gao J, He S, Zhang Y, Wang Q. An evaluation on the efficacy and safety of treatments for attention deficit hyperactivity disorder in children and adolescents: a comparison of multiple treatments. *Mol Neurobiol*. 2016 Oct 13.[Epub ahead of print].
- McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: Results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251-1260.
- Metadate CD [package insert], Smyrna, GA: UCB; January 2017.
- Methylin oral solution [package insert], Florham Park, NJ: Shionogi Inc.; September 2016.
- Methylphenidate chewable tablets [package insert]: Somerset, NJ: GAVIS Pharmaceuticals, LLC; December 2015.
- Methylphenidate ER [package insert], Newtown, PA: KVK-Tech, Inc.; July 2015.
- Methylphenidate hydrochloride extended-release tablets (generic Concerta) made by Mallinckrodt and Kudco. FDA Web site. November 4, 2016. http://www.fda.gov/Drugs/DrugSafety/ucm422568.htm. Accessed June 23, 2017.
- Morgenthaler TI, Kapur VK, Brown T, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30(12):1705-1711.
- Mydayis [package insert], Lexington, MA: Shire US Inc.; June 2017.
- Newcorn JH, Kratochvil CJ, Allen AJ, et al; Atomoxetine/Methylphenidate Comparative Study Group. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. *Am J Psychiatry*. 2008;165(6):721-730.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 23, 2017.
- PL Detail-Document, Comparison of ADHD medications. *Pharmacist's Letter/Prescriber's Letter*. March 2016
- PL Detail-Document, Management of ADHD: When a stimulant is not enough . *Pharmacist's Letter/Prescriber's Letter*. April 2015.
- Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
- Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341-1359.
- ProCentra [package insert], Newport, KY: Independence Pharmaceuticals, LLC; February 2017.
- Punja S, Shamseer L, Hartling L, et al. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Syst Rev*. 2016;2:CD009996.
- QuilliChew ER [package insert], New York, NY: Pfizer, Inc.; March 2017.
- Quillivant XR [package insert], New York, NY: Pfizer, Inc.; June 2017.
- Ritalin [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2017.
- Ritalin LA [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation.; January 2017.
- Scammell TE. Treatment of narcolepsy in adults. UpToDate Web site. 2017. http://www.uptodate.com. Updated June 21, 3017. Accessed June 23, 2017.
- Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):174-187.
- Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2015;11:CD009885.
- Strattera [package insert], Indianapolis, IN: Lilly USA, Inc.; May 2017.
- Stuhec M, Munda B, Svab V, Locatelli I. Comparative efficacy and acceptability of atomoxetine, lisdexamfetamine, bupropion and methylphenidate in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis with focus on bupropion. *J Affect Disord*. 2015;178:149-159.
- Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1122.
- Vyvanse [package insert], Lexington, MA: Shire US Inc.; May 2017.
- Yager J, Devlin MF, Halmi KA, et al. Guideline watch (August 2012): Practice guideline for the treatment of patients with eating disorders, 3rd edition. Psychiatry Online Web site. http://psychiatryonline.org/guidelines. Accessed June 23, 2017.
- Yager J, Devlin MF, Halmi KA, et al. Practice guideline for the treatment of patients with eating disorders, 3rd edition (2006). Psychiatry Online Web site. http://psychiatryonline.org/guidelines. Accessed June 23, 2017.
- Zenzedi [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; February 2017.

Therapeutic Class Overview
Atypical Antipsychotics

INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications exert their effect in part by blocking D2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with schizophrenia (*Farah 2005*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first generation antipsychotics (FGAs), and atypical antipsychotics, also called second generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Clinical Pharmacology 2017*).
  - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole acts as a partial agonist at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Brexpiprazole and cariprazine are partial agonists at D-2 and 5-HT1A receptors and antagonists at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, and schizoaffective disorder:
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman and Bridgemohan 2017*).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the United States report a prevalence of 14.6 per 1000 children at age 8 in 2012 (*Morbidity and Mortality Weekly Report [MMWR] 2016*).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component which alters brain development (*Augustyn 2017*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman and Bridgemohan 2017*).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be approximately 1%, although the true prevalence is uncertain (*Stovall 2017[a]*).
  - Genetics, in addition to environmental factors, appears to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2017[b]*).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Gelenberg et al 2010*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2006 to 2008, approximately 9% of US adults meet the criteria for current depression, including 3.4% who have MDD. Women are more likely to experience major depression in their lifetime as compared to men (11.7 vs 5.6%), and major depression is most prevalent in patients aged 45 to 64 years old (*CDC 2013, MMWR 2010*).

- Schizophrenia
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Lehman et al 2004*).
  - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013*, *Lehman et al 2004*).
  - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
  - The prevalence of schizophrenia is approximately 0.3 to 0.66%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008*, *van Os et al 2009*).
- Tourette's disorder
  - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
  - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
  - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
  - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school age children having had tics in the previous year.
- The agents included in this review are listed in Table 1 by brand name. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
  - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole)	✔ *
Abilify Discmelt (aripiprazole)	✔ *
Clozaril (clozapine)	✔
Fanapt (iloperidone)	-†
Fazaclo (clozapine)	✔
Geodon (ziprasidone hydrochloride [HCl])	✔
Geodon (ziprasidone mesylate)	-
Invega (paliperidone extended-release [ER])	✔

Drug	Generic
Latuda (lurasidone)	-
Rexulti (brexpiprazole)	-
Risperdal (risperidone)	✔
Risperdal M-Tab (risperidone)	✔
Saphris (asenapine)	-
Seroquel (quetiapine)	✔
Seroquel XR (quetiapine ER)	✔
Versacloz (clozapine)	-
Vraylar (cariprazine)	-
Zyprexa (olanzapine)	✔
Zyprexa Zydis (olanzapine)	✔
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Risperdal Consta (risperidone microspheres)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine)	✔

*Brand Abilify oral solution and orally disintegrating tablets have been discontinued; generic products are available.
†Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products (*ME staff press release, 2016*).

(*Drugs@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

- The following summarizes all FDA-approved indications:
  - Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
  - Bipolar disorder: All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. Risperidone long-acting injection is the only long-acting injectable indicated for the treatment of bipolar disorder.
    - Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
  - Depression: Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment resistant depression.
  - Schizophrenia: All agents in class are indicated for use in schizophrenia with the exception of the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia.
    - Aripiprazole, lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.

- Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.

- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder
Single Entity Products									
aripiprazole	✔ *	✔ *	-	-	✔	-	✔ *	-	✔ *
asenapine	-	✔ *	-	-	-	-	✔	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-
clozapine	-	-	-	-	-	✔	-	✔	-
iloperidone	-	-	-	-	-	-	✔	-	-
lurasidone	-	-	✔	-	-	-	✔ *	-	-
olanzapine	-	✔ *	-	-	-	-	✔ *#	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-
ziprasidone HCl	-	✔	-	-	-	-	✔	-	-
ziprasidone mesylate	-	-	-	-	-	-	✔ §	-	-
Long-Acting Injectable Products									
aripiprazole ER	-	-	-	-	-	-	✔	-	-
aripiprazole lauroxil ER	-	-	-	-	-	-	✔	-	-
paliperidone palmitate (Invega Sustenna)	-	-	-	-	-	✔	✔	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✔	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-
olanzapine pamoate	-	-	-	-	-	-	✔ ‡	-	-
Combination Products									
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	

*FDA-approved indications for pediatric patients; †ER formulation; ‡ Patients must be observed by a health care professional for 3 hours post-dose administration; § intramuscular (IM) injection indicated for acute agitation associated with schizophrenia; #IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.

(Prescribing information: *Abilify 2017, Abilify Maintena 2017, Aristada 2017, Clozaril 2017, Fanapt 2017, Fazaclo 2017, Geodon 2017, Invega 2017, Invega Sustenna 2017, Invega Trinza 2017, Latuda 2017, Rexulti 2017, Risperdal 2017, Risperdal Consta 2017, Saphris 2017, Seroquel 2017, Seroquel XR 2017, Symbyax 2017, Versacloz 2017, Vraylar 2017, Zyprexa 2017, Zyprexa Relprevv 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SR), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

The Agency for Healthcare Research and Quality (AHRQ) conducted an SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 for placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points for 5 mg/day, 2.5 for 10 mg/day, and 2.5 for 15 mg/day compared with 3.3 for placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (*Hirsch et al 2016*).
- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy

(*Risperdal prescribing information 2017*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7kg vs 1 kg), pulse rate, and systolic blood pressure.

- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients per trial. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean baseline ABC-I subscale was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo, asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in YMRS score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures

were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; p = 0.25). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).

- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; p = 0.003). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a Young Mania Rating Scale (YMRS) item 1 score ≤ 2) vs 59.2% of placebo group patients (p = 0.003). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; p < 0.001), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all p < 0.001). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo (p < 0.001) and increase in heart rate was also statistically significantly higher in the treatment group (p = 0.013). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).
- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and higher glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).

- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 in placebo (*Abilify prescribing information 2017*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2017*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. The following summarizes direct comparative evidence and recent MAs and SRs.
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients

and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).

- An SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapses; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 5 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). An MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (*McIntyre et al 2009[b]*).
- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2014*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2014*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, the steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint).

Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

Depressive Episodes

- PC trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- MAs have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Ostacher 2017*, *Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

Major Depressive Disorder (MDD)

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics treatment in combination with a SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8

weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients, 50 to 67 years and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al 2005*). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).
- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) dose significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but the quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day dose (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo treatment, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in class indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (p < 0.001) (*Thase et al 2007*). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine,

olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

Schizophrenia and/or Schizoaffective Disorder

- All oral atypical antipsychotic agents in class are indicated for use in schizophrenia with the exception of combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following summarizes recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, Iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).
- One large, recent Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approve agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There is limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with

fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year (*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al,2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (*Kane et al 2011*). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (*Shoemaker et al 2010*). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (Hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and

included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible dose study with no active comparator. In the flexible dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[bJ*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95%CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; p < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of Iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (p = 0.85), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; p < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (p < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone dosed 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-

S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day), or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperidone long-acting injection is the only long-acting injection FDA-approved for bipolar I disorder as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Mcfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Mcfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Mcfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 6 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada (aripiprazole lauroxil), Zyxprexa Relprevv (olanzapine pamoate), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Risperdal Consta (risperidone microspheres). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (p = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (p < 0.001) and oral antipsychotics (p = 0.048) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; p = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (p = 0.02)

and in preventing hospitalization (p = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (p = 0.65) (*Kishimoto et al 2013*).

- One MA compared outcomes for once-monthly long acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5% to 16%) (*Gentile et al 2013*).
- Two additional long-acting injectable agents were approved in 2015, Aristada (aripiprazole lauroxil) and Invega Trinza (paliperidone palmitate once-every-3-months injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly intramuscular (IM) injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL/DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once every 3 month injection. Paliperidone palmitate once every 3 months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), weight increased (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%) (*Berwaerts et al 2015*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

  Adults
  - Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010*).
    - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
    - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).

- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*; *Gelenberg et al 2010*).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009; Lehman et al 2004; VA Pharmacy Benefits Management Services 2012*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or is taking drugs that have demonstrated QT prolongation. Lurasidone is contraindicated for concomitant use with strong CYP3A4 inducers and/or inhibitors. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- All atypical antipsychotic agents have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, and olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome. Lastly, clozapine-containing agents (ie, Clozaril, Fazaclo, and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors
  - Clozapine-containing products: Hepatotoxicity, QT prolongation, pulmonary embolism, fever, and anticholinergic toxicity
  - Iloperidone: QT prolongation, hyperprolactinemia, and priapism

  - Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Lurasidone: Hyperprolactinemia
  - Risperidone: Priapism and hyperprolactinemia
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, and hyperprolactinemia
  - Olanzapine: DRESS and hyperprolactinemia
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling is required as part of both programs (*REMS@FDA 2017*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is unknown (*FDA safety communication [clozapine] 2016*).
  - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with iloperidone, olanzapine, and ziprasidone.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Moderate	Low	Moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Negligible	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate
Hypercholesterolemia	Negligible	Negligible	Low	Negligible to low	Very high	Moderate	Negligible to low	Very high	Low	High	Low	Negligible to low

Abbrv: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson et al 2017*)

DOSING AND ADMINISTRATION

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablets, orally disintegrating tablets, oral solution	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Saphris (asenapine)	Sublingual tablets	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Rexulti (brexpiprazole)	Tablets	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsules	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablets	Oral	Daily up to divided doses daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment,
Fazaclo (clozapine)	Orally disintegrating tablets			

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Versacloz (clozapine)	Suspension			CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Fanapt (iloperidone)	Tablets	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Latuda (lurasidone)	Tablets	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Should be administered with food (≥ 350 calories).
Zyprexa (olanzapine)	Tablets	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablets			
Zyprexa (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsules	Oral	Daily	
Invega (paliperidone ER)	Tablets	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.
Seroquel (quetiapine)	Tablets	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablets	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablets, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablets			
Risperdal Consta (risperidone)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Geodon (ziprasidone)	Capsules	Oral	Twice daily	IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (*Miyamato et al 2005*).
- There are a number of atypical antipsychotics formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder, schizophrenia, and schizoaffective disorder. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in class are indicated for use in schizophrenia with the exception of combination agent Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine is the only

agent in class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and brexpiprazole. Risperidone long-acting injection is the only long-acting injectable indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Lehman et al 2004, Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012, Clinical Pharmacology 2017*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2017; Micromedex 2017*). The following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in class; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
  - Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia

have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, and lurasidone. However, fewer studies have been conducted with the newer agents.
  - Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
  - Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
  - Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
  - Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
  - Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.
- Newly FDA-approved agent, cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2014*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2017*, *Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in placebo controlled trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and

aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).

- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (*Findling et al 2014, Detke et al 2015*). Support for use of atypical antipsychotics in adult patients with bipolar disorder have been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta is the only long-acting injection agent in class that has demonstrated safe and effective use (*McFadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011*).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

<u>Adults</u>

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010*).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*, *Gelenberg et al 2010*).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012*).

<u>Children and Adolescents</u>

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic

assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
    - Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
    - Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
    - Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
    - Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

REFERENCES

- Abilify [package insert]. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; February 2017.
- Abilify Maintena [package insert].. Princeton, NJ: Otsuka America Pharmaceutical, Inc; February 2017.
- Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation and second-generation antipsychotics in adults: Comparative Effectiveness Review. [Monograph on the internet]. Agency for Healthcare Research and Quality (AHRQ). Rockville, MD. 2012 Aug. No. 63. http://www.ncbi.nlm.nih.gov/books/NBK42934/. Accessed June 29, 2017.
- Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. *J Child Adolesc Psychopharmacol*. 2008;18(3):227-236.
- American Psychiatric Association. Diagnostic and Statistical manual of Mental Disorders, 5th edition (DSM V). Washington, DC: In Section II, Depressive Disorders and Schizophrenia Spectrum and Other Psychotic Disorders. May 2013.
- Aristada [package insert]. Waltham, MA: Alkermes, Inc.; June 2017.
- Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(11):CD006633.
- Asmal A, Flegar SJ, Wang J, et al. Quetiapine versus other atypical anti*p*sychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013:11:CD006625.
- Augustyn, M. Autism spectrum disorder: terminology, epidemiology, and pathogenesis. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomized, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *Journal of Affective Disorders*. 2010;127:19-30.
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843-853.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia. *JAMA Psychiatry*. 2015;72(8):830-839.
- Biederman J, McDonnel MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectrums*. 2005;10(2):141-148.
- Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar depression. Int J *Neuropsychopharmaco*l. 2009;12:773-782.
- Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; 76(3):284-292.
- Capone GT, Goyal P, Grados M, et al. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: a naturalistic study. *J Dev Behav Pediatr*. 2008;29:106-116.
- Centers for Disease Control and Prevention (CDC). Burden of Mental Illness. October 4, 2013. https://www.cdc.gov/mentalhealth/basics/burden.htm. Accessed June 29, 2017.

- Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2012;27(2):76-90.
- Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. *Schizophrenia Research*. 2011;131:75-81.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol Clin Exp*. 2012;27:24-32.
- Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63(12):1762-1784.
- Clinical Pharmacology Web site. 2017. http://www.clinicalpharmacology-ip.com. Accessed June 29, 2017.
- Clozaril [package insert]. Rosemont, PA: HLS Therapeutics; February 2017.
- Correll CU, Manu P, Olshanskiy V, et al. Cardiovascular risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.
- Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(9):870-880.
- Corya SA, Williamson D, Sanger TM, et al . A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006;23:364-372.
- Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20-28.
- DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11:483-93.
- Detke HC, DelBello, MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-224.
- Dixon L, Perkins D, Calmes C; for the American Psychiatric Association. Guideline Watch (September 2009): Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia-watch.pdf. Accessed June 29, 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. 2017. http://www.accessdata.fda.gov/scripts/cder/daf. Accessed June 29, 2017.
- Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015 [a]; 76(12):e1574-1582.
- Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2016;176(2-3):264-271.
- Durgam S, Greenberg WM, Li D, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234(2):199-209.
- Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.
- Durgam S, Starace A, Migliore R, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015[b];17(1):63-75.
- Fanapt [package insert]. Washington, D.C.: Vanda Pharmaceuticals Inc.; February 2017.
- Farah A. Atypicality of atypical antipsychotics. *Prim Care Companion J Clin Psychiatry*. 2005;7:268-274.
- Fazaclo [package insert]. Palo Alto, CA: Jazz Pharmaceuticals; February 2017.
- FDA and Center for Drug Evaluation and Research (CDER). Summary Review: Vraylar (cariprazine). Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf . September 17, 2015. Accessed June 29, 2017.
- FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Food and Drug Administration Web site. http://www.fda.gov/drugs/drugsafety/ucm461853.htm. September 15, 2015. Accessed June 29, 2017.
- FDA Drug Safety Communication: FDA working with manufacturers to resolve challenges with the Clozapine REMS program. Food and Drug Administration Web site. http://www.fda.gov/drugs/drugsafety/ucm467560.htm. December 16, 2016. Accessed June 29, 2017.
- Findling RL, Drury SS, Jensen PS, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents. Approved by the AACAP Council on August 2, 2011. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf. Accessed June 29, 2017.
- Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041.
- Findling RL, Pathak S, Earley W, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325-335.
- Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsycholpharmacol*. 2016.pii:pyw076.
- Fornaro M, Stubbs B, De Barardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016;17(2):241.
- Fusar-Poli P, Kempton MJ, Rosenheck RA. Efficacy and safety of second-generation long-acting injections in schizophrenia: A meta-analysis of randomized-controlled trials. *Int Clin Psychopharmacol*. 2013;28(2):57–66.
- Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):39-47.

- Gelenberg AJ, Freeman MP, Markowitz JC, et al; for the American Psychiatric Association Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder. Third edition. Arlington, VA; 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed June 29, 2017.
- Gencer O, Emiroglu FNI, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: an open-label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;217-225.
- Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. *Pharmacotherapy*. 2013;33(10):1087-1106.
- Geodon [package insert]. New York, NY: Pfizer Pharmaceuticals; February 2017.
- Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
- Glick ID, Correll CU, Altamura AC, et al. Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data driven, personalized clinical approach. *J Clin Psychiatry*. 2011;72(12):1616-1627.
- Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-Week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017 May 5. doi:10.1089/cap.2016.0189. [Epub ahead of print]
- Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurolo Sci*. 2011;32(6):1213-1217.
- Hamilton Depression Rating Scale. Food and Drug Administration Web site. 2007. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_04-DescriptionofMADRSHAMDDepressionR(1).pdf. Accessed June 29, 2017.
- Harvey PD, Ogasa M, Cucchiaro, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone. *Schizophrenia Research*. 2011;127:188-194.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016;(6):CD009043.
- Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder [monograph on the internet]. Arlington (VA): American Psychiatric Association; April 2002. http://psychiatryonline.org/guidelines. Accessed June 29, 2017.
- Hirschfeld RMA; for the American Psychiatric Association. Guideline Watch: Practice guideline for the treatment of patients with bipolar disorder, 2nd ed. Arlington (VA): American Psychiatric Association; November 2005. http://psychiatryonline.org/guidelines. Accessed June 29, 2017.
- Invega [package insert]. Titusville, NJ: Janssen Pharmaceuticals. February 2017.
- Invega Sustenna [package insert]. Titusville, NJ: Janssen Pharmaceuticals. Titusville, NJ; June 2017.
- Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Jibson MD, Marder S, Herman R. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Jones MP, Nicholl D, Trakas K, et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. Int J Clin *Pharmacol Ther*. 2010;48(6):383-399.
- Kamijima K, Higuchi T, Ishigooka J, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). *J Affect Disord*. 2013;151(3):899-905.
- Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010[a];30:106-115.
- Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry*. 2010[b];167:181-189.
- Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from three clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S29-S35.
- Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
- Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015[a];164(1-3):127-135.
- Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015[b]; 35(4):367-373.
- Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2014;1:CD006569.
- Kishimoto T, Robenzadeh A, Leucht S, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192–213.
- Klemp M, Tvete IF, Skomedal T, et al. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of four atypical neuroleptic drugs compared to haloperidol and placebo. *J Clin Psychopharmacol*. 2011;31:698-704.
- Komossa K, Depping AM, Gaudchau A, et al. Second-generation antipsychotics for major depressive disorder and dysthymia. *Cochrane Database of Systematic Reviews*. 2010[c]; (12): CD008121.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [a];(3):CD006654.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*. 2009[b]; (4): CD006627.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Quetiapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [b];(1):CD006625.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Risperidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2011;(1):CD006626.
- Komossa K, Rummel-Kluge, Schmid F, et al. Aripiprazole vs other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*. 2009[a];4:CD006569.
- Kumar A, Datta S, Wright S, et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev*. 2013 Oct 15;10:CD009582.

- Latuda [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; February 2017.
- Lehman AF, Lieberman JA, Dixon LB, et al; for the American Psychiatric Association Work Group on Schizophrenia. Practice guideline for the treatment of patients with schizophrenia. Second edition. Arlington, VA; 2004. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Accessed June 29, 2017.
- Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:2404-2412.
- Leucht S, Cipraini A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382: 951-962.
- Leucht S, Corves C, Arbter D, et al. Second-generation vs first-generation drugs for schizophrenia: a meta-analysis. *Lancet*. 2009[a];373:31-41.
- Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009[b];166:152-163.
- Lieberman JA, Stroup TS, McElvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord*. 2017 ;213:138-150.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[a];171(2):169-177.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014[b];171(2):160-168.
- Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.
- Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156-165
- Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
- Marcus RN, Owen R, Manos G, et al. Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. *J Clin Psychiatry*. 2011;72(9):1270-1276.
- Market Exclusive (ME) staff. Vanda Pharmaceuticals, Inc (NASDAQ:VNDA) Files An 8-K Other Events. [press release]. December 20, 2016. Available at: https://marketexclusive.com/vanda-pharmaceuticals-inc-nasdaqvnda-files-an-8-k-other-events-2/49544/. Accessed June 29, 2017.
- McClellan J, Kowatch R, Findling RL, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolec Psychiatry*. 2007;46(1):107-125.
- McClellan J, Stock S; for the American Academy of Children and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolec Psychiatry*. 2013;52(9):976–990.
- McCracken JT, McGough J, Shah J, et al. Risperidone in children with autism and serious behavioral problems (RUPP). *N Engl J Med*. 2002;347:314-321.
- McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry*. 2005;162:1142-1148.
- Mcfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009;11(8):827-839.
- McGrath J, Saha S, Chant D, et al. Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76.
- McIntyre RS, Cohen M, Zhao J, et al. A three-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disorders*. 2009[a];11:673-686.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010[b];126:358-365.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010[a];122:27-38.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine vs olanzapine in acute mania: a double-blind extension study. *Bipolar Disorders*. 2009[b];11:815-826.
- Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.
- Meltzer L, Risinger R, Nasrallah M, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090.
- Micromedex Solutions Web site. 2017. http://www.micromedexsolutions.com/home/dispatch. Accessed June 29, 2017.
- Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone vs haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1-8.
- Miyamato S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry*. 2005;10:79-104.
- Morbidity and Mortality Weekly Report (MMWR). Current Depression Among Adults – United States, 2006 and 2008. *MMWR Weekly*. 2010; 59(38):1229-1235.
- Morbidity and Mortality Weekly Report (MMWR). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012. *MMWR Weekly*. 2016 65(3);1-23.
- Muralidharan K, Ali M, Silveira LE, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *J Affect Disord*. 2013;150(2):408-414.
- Murphy TK, Lewin AB, Storch EA, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341–1359.

- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455.
- Nakamura M, Ogasa MS, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-836.
- Nussbaum A and Stroup T. Paliperidone palmitate for schizophrenia. *Cochrane Database Syst Rev*. 2012;6:CD008296.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 29, 2017.
- Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. *World J Biol Psychiatry*. 2017:1-11.
- Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533-1540.
- Pagsberg AK, Tarp S, Glintborg D, et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):191-202.
- Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin-reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005; 66(10):1326-1330.
- Perlis RH, Baker RW, Zarate CA, et al. Olanzapine vs risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006[a];67:1747-1753.
- Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006[b];76:509-516.
- Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: Systematic review update. Comparative Effectiveness Review No. 184. AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. www.effectivehealthcare.ahrq.gov/reports/final/cfm. doi: https://doi.org/10.23970/AHRQEPCCER184. Accessed June 29, 2017.
- Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68:1492-1500.
- Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase three studies. *J Clin Psychopharm*. 2008;28:S4-S11.
- Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2011;132:101-107.
- Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010;68(2):156-162.
- REMS@FDA . Food and Drug Administration Web site. 2017. http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed June 29, 2017.
- Rexulti [package insert]. Rockville, MD: Otsuka Pharmaceuticals Co., Ltd; February 2017.
- Riedel M, Schennach-Wolff R, Dehning MS, et al. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum Psychopharmacol Clin Exp*. 2010; 25:116-125.
- Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2017.
- Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.
- Saphris [package insert]. St. Louis, MO: Forest Pharmaceuticals; February 2017.
- Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010; 43:e1-e10.
- Seroquel [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2017.
- Seroquel XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. February 2017.
- Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Phsychopharm*. 2011;26:130.
- Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634-e641.
- Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/ fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry*. 2005;66:1289-1297.
- Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013:146(3):310-318.
- Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med.* 2013;10(3):e1001403. doi: 10.1371/journal.pmed.1001403.
- Steffens DC, Nelson JC, Eudicone JM, et al: Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. *Int J Geriatr Psychiatry*. 2011; 26(6):564-572.
- Stovall J. Bipolar disorder in adults: epidemiology and pathogenesis. UpToDate Web site. 2017[a]. www.uptodate.com/. Accessed June 29, 2017.
- Stovall J. Bipolar disorder in adults: Pharmacotherapy for acute mania and hypomania. UpToDate Web site. 2017[b]. www.uptodate.com/ . Accessed June 29, 2017.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Results of phase three of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1-12.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611-622.
- Symbyax [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2017.
- Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101.

- Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77.
- Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania-a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011;134:14-19.
- Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):452-469.
- Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
- Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015[b];76(9):1232-1240.
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015[a];76(9):1224-1231.
- Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.
- Van Os J, Kapur S. Schizophrenia. *Lance*t. 2009;374(9690):635-645.
- Versacloz [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; February 2017.
- Veterans Administration (VA) and Department of Defense (DoD) Clinical Practice Guideline for Management of Major Depressive Disorder. VA/DoD Web site. April 2016. http://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed June 29, 2017.
- Veterans Administration (VA) Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives. Recommendations for antipsychotic selection in schizophrenia and schizoaffective disorders. June 2012. http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations.asp. Accessed June 29, 2017.
- Veterans Administration (VA) Pharmacy Benefits Management Services; for the Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010 May. 176 p. http://www.healthquality.va.gov/bipolar/bd_305_full.pdf. Accessed June 29, 2017.
- Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30:579-590.
- Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257.
- Vraylar [package insert]. Irvine, CA: Allergan USA, Inc.; February 2017.
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. A pooled analysis of six-week acute-phase pivotal trials. *J Clin Psychopharmacol*. 2008;28:S12-S19.
- Weiden PJ, Manning R, Wolfgang CD, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. *CNS Drugs*. 2016;30(8):735-747.
- Weissman L, Bridgemohan C. Autism spectrum disorders in children and adolescents: overview and management. UpToDate Web site. 2017. www.uptodate.com/. Accessed June 29, 2017.
- Wen XJ, Wang LM, Liu ZL, et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Braz J Med Res*. 2014;47(7):605-616.
- Yatham LN, Fallu A, Binder CE. A six-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007;(434):50-56.
- Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011;36:375-389.
- Yoo HK. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-e780.
- Yoon S, Jeon SW, Ko YH, et al. Adjunctive brexpiprazole as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2017;37(1):46-53.
- Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150-162.
- Zyprexa Relprevv [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.
- Zyprexa Zydis [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.
- Zyxprexa [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.

Therapeutic Class Overview
Leukotriene Modifiers

INTRODUCTION

- The leukotriene modifiers can be divided into two pharmacologic categories: the leukotriene receptor antagonists, zafirlukast (ACCOLATE®) and montelukast (SINGULAIR®), and the 5-lipoxygenase inhibitors, zileuton (ZYFLO®) and zileuton extended-release (ZYFLO CR®). The leukotriene modifiers are all Food and Drug Administration (FDA)-approved for prophylaxis and chronic treatment of asthma. Montelukast carries additional indications for the relief of symptoms of seasonal and perennial allergic rhinitis and for the prevention of exercise-induced bronchoconstriction (Drugs@FDA, 2017).
- Currently, montelukast, zileuton extended-release (ER), and zafirlukast are available generically. Montelukast is available in tablets, chewable tablets, and oral granules. Zafirlukast is available in tablets. Zileuton is available as immediate-release and extended-release tablets (Drugs@FDA, 2017).
- Treatment guidelines generally position leukotriene modifiers not as first-line agents, but rather as alternatives or additive therapy to other classes of medications for the treatment of asthma, allergic rhinitis, and exercise-induced bronchospasm.
- For asthma, inhaled corticosteroids (ICSs) are first-line therapy for control of persistent asthma; leukotriene modifiers may be used as alternatives to ICSs or the addition of a leukotriene receptor antagonist may assist patients stepping down from low-dose ICS in mild asthma; it may also be used as additive therapy to ICSs in moderate to severe asthma (National Heart, Lung, and Blood Institute [NHLBI], 2007; Global Initiative for Asthma [GINA], 2017).
- For allergic rhinitis, intranasal corticosteroids are the most effective medication class, and antihistamines are also effective. Leukotriene modifiers may be used as alternatives or in combination with other agents, but are not as effective as intranasal corticosteroids (Wallace et al, 2008; Snellman et al, 2013).
- Although β_2-agonists are the most effective agents for the prophylaxis and relief of exercise-induced bronchoconstriction, daily use of β_2-agonists can lead to tolerance. Leukotriene modifiers can be considered as a daily therapy option as their use does not lead to tolerance. However, leukotriene modifiers do not provide complete protection against exercise-induced bronchoconstriction as they are not effective at reversing airway obstruction (Weiler et al, 2016). Leukotriene modifiers may be an option in patients with exercise-induced bronchoconstriction who have persistent symptoms despite using a short-acting β_2-agonist before exercise, or who require an inhaled short-acting β_2-agonist daily or more frequently (Parsons et al, 2013).
- Medispan class: Leukotriene Modifiers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SINGULAIR (montelukast)	Merck & Co., Inc.	02/20/1998*	✔
ACCOLATE (zafirlukast)	AstraZeneca Pharmaceuticals LP	09/26/1996	✔
ZYFLO (zileuton)	Chiesi USA Inc.	12/09/1996	-
ZYFLO CR (zileuton ER)	various	05/30/2007	✔

*07/26/2002 for the oral granule dosage form

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	SINGULAIR (montelukast)	ACCOLATE (zafirlukast)	ZYFLO, ZYFLO CR (zileuton)
Prophylaxis and chronic treatment of asthma	✔ (age ≥12 months)	✔ (age ≥5 years)	✔ (age ≥12 years)
Acute prevention of exercise-induced bronchoconstriction	✔ (age ≥6 years)		
Relief of symptoms of perennial allergic rhinitis	✔ (age ≥6 months)		
Relief of symptoms of seasonal allergic rhinitis	✔ (age ≥2 years)		

(Prescribing information: ACCOLATE, 2013; SINGULAIR, 2016; ZYFLO, 2014; ZYFLO CR, 2017)

Information on indications, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Clinical Trials

- There are numerous placebo-controlled trials examining the efficacy of the leukotriene modifiers for asthma. When compared to placebo, leukotriene modifiers demonstrated efficacy in most aspects of asthma control, including pulmonary function, asthma symptoms, β_2-agonist use, asthma exacerbations and nighttime symptom control (Virchow et al, 2010(a); Virchow et al, 2010(b); Knorr et al, 1998; Reiss et al, 1998; Visitsunthorn et al, 2011; Yildirim et al, 2004; Price et al, 2003; Bozek et al, 2012; Chen et al, 2014).
- There is also a large body of clinical data comparing the leukotriene modifiers to inhaled corticosteroids and long-acting β_2-agonists. When compared to these other long-term controller medications, the leukotriene modifiers have not demonstrated equivalence or significant advantages in clinical outcomes (Szefler et al, 2005; Zeiger et al, 2006; Garcia et al, 2005; Busse et al, 2001; Sorkness et al, 2007; Bjermer et al, 2003; Calhoun et al, 2001; Maspero et al, 2008; Lemanske et al, 2010; Fish et al, 2001; Wilson et al, 2010(a); Wilson et al, 2010(b); Ducharme et al, 2006; Suissa et al, 1997; Busse et al, 1999; Israel et al, 1996; Israel et al, 1993; Nelson et al, 2007; Wenzel et al, 2007).
- Leukotriene modifiers have not been adequately studied in comparison to one another. However, in one randomized, open-label, comparative multicenter clinical trial, results suggest that zileuton ER has better therapeutic efficacy for the treatment of asthma in comparison to montelukast as shown by changes in peak expiratory flow rate (PEFR) and mean overall symptom intensity score (Kubavat et al, 2013).
- According to a 2013 Cochrane review, there is no firm evidence to support that adding montelukast to an ICS is safe and effective to reduce the occurrence of moderate or severe asthma attacks in children taking a low-dose ICS and whose symptoms remain uncontrolled. After being on the market for more than 10 years, the limited number of available studies testing antileukotrienes in children, the absence of data on preschoolers, and the inconsistency of available trials in reporting of efficacy and safety clinical outcomes is disappointing and limit the conclusions (Chauhan et al, 2013).
- With regard to allergic rhinitis, montelukast has been shown to be more effective than placebo and has demonstrated comparable efficacy to second-generation antihistamines; however, it has not been shown to be as effective as intranasal corticosteroids (Cingi et al, 2010; Li et al, 2009; Esteitie et al, 2010; Baena-Cagnani et al, 2003; Meltzer et al, 2000; Saengpanich et al, 2003; Pullerits et al, 2002; Mucha et al, 2006; Wasfi et al, 2011; Wei, 2016).
- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of seasonal allergic rhinitis. A total of 59 randomized controlled trials met inclusion criteria to compare agents of six classes for relative efficacy. Agents included oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of seasonal allergic rhinitis. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination

of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. No information was available about the use of these agents for the treatment of seasonal allergic rhinitis in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).

- Montelukast has also been shown to be more effective than placebo in preserving pulmonary function in patients with exercise-induced bronchoconstriction (Wasfi et al, 2011).

Treatment Guidelines

- Treatment guidelines published by NHLBI recommend the use of ICSs as first-line therapy for long-term control of persistent asthma symptoms in children and adults. All three leukotriene modifiers can be used as alternative adjunctive agents to low- and medium-dose ICS; however, they are not recommended as preferred agents (NHLBI, 2007).
- The Global Initiative for Asthma (GINA) guidelines recommend that leukotriene receptor antagonists be used as alternative agents to low-dose ICSs. The leukotriene receptor antagonists are particularly appropriate in patients who are unable or unwilling to use ICSs, in those who experience intolerable adverse events on ICS therapy, or in patients with concomitant allergic rhinitis. The leukotriene receptor antagonists are also recommended as add-on treatment to ICS agents; however, the benefit reported with this treatment combination has been shown to be less than that of a combination of ICS and LABA. When good asthma control is established, leukotriene receptor antagonists may be used to allow tapering of low-dose ICSs in mild asthma. Completely stopping ICSs are not recommended, however, as it is associated with higher risk of exacerbations (GINA, 2017).
- The Joint Task Force on Practice Parameters for Allergy and Immunology recommends intranasal corticosteroids as the most effective medication class for controlling symptoms of allergic rhinitis, and all are considered equally efficacious. It is also suggested that intranasal antihistamines be considered as first-line treatment for both allergic and non-allergic rhinitis. The leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis (Wallace et al, 2008).
- The Institute for Clinical Systems Improvement (ICSI) guidelines notes that intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered as first-line therapy in patients with moderate to severe symptoms. Antihistamines and cromolyn can be considered as alternatives in patients who prefer not to use intranasal corticosteroids. Antihistamines are somewhat less effective than intranasal corticosteroids; however, oral antihistamines are effective alternatives in patients who cannot use or prefer not to use intranasal corticosteroids. Leukotriene modifiers are as effective as second-generation antihistamines for the treatment of allergic rhinitis; however, they are not as effective as intranasal corticosteroids (Snellman et al, 2013). According to a recent clinical practice guideline from the American Academy of Otolaryngology-Head and Neck Surgery, leukotriene modifiers should not be recommended as the first-line therapy for patients with allergic rhinitis because they are as effective or less effective than oral antihistamines and intranasal corticosteroids; however, they may be an appropriate primary therapy for certain patients who have asthma and allergic rhinitis (Seidman et al, 2015).
- An American Thoracic Society guideline states that for patients with exercise-induced bronchoconstriction, administration of a short-acting β_2-agonist before exercise is recommended. A controller agent is generally added when the short-acting β_2-agonist is used daily or more frequently. For patients with exercise-induced bronchoconstriction who continue to have symptoms despite use of a short-acting β_2-agonist before exercise, or who require a short-acting β_2-agonist daily or more frequently, options include adding daily use of an ICS, daily use of a leukotriene modifier, or the use of either a mast cell stabilizer or an inhaled anticholinergic agent before exercise (Parsons et al, 2013).
- The American Thoracic Society acknowledges leukotriene modifiers may provide benefit for the treatment of asthma in elderly patients. The management of asthma is based on the guidelines for younger patients, as there are not many studies that included older patients with asthma. ICS is the controller therapy of choice for asthma in elderly. From the few studies available, using leukotriene modifiers for asthma in elderly improved asthma indices, but it was not as pronounced as in younger patients. Also, the improvements seen with leukotriene modifiers were less than the improvements seen with ICSs for the elderly (Skloot et al, 2016).
- The Joint Task Force on Practice Parameters for Allergy and Immunology recommends β_2-agonists as the most effective agents for the prophylaxis and relief of exercise-induced bronchoconstriction; however, daily use of β_2-agonists may lead to tolerance. The use is therefore recommended only on an intermittent basis for the prevention of exercise-induced bronchoconstriction. Leukotriene receptor antagonists may be used daily or intermittently for the

prevention of exercise-induced bronchoconstriction without development of tolerance; however, these agents do not reverse airway obstruction when it occurs (Weiler et al, 2016).

SAFETY SUMMARY

- All leukotriene modifiers are contraindicated in patients with known hypersensitivity and/or allergic reaction to the medication or components of the product. In addition, both zafirlukast and zileuton have contraindications related to hepatic insufficiency. Zafirlukast is contraindicated in patients with hepatic impairment, including cirrhosis. Zileuton is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal.
- Key warnings and precautions include:
    - Leukotriene modifiers are not indicated for reversal of acute asthma attacks.
    - All leukotriene modifiers may cause neuropsychiatric events.
    - Zileuton has several drug interactions; it may increase the plasma activity of propranolol, theophylline, and warfarin. Zafirlukast may increase the activity of warfarin.
    - Patients taking montelukast or zafirlukast should be monitored for signs and symptoms of systemic eosinophilia.
    - Hepatotoxicity may occur with zafirlukast or zileuton.
- The most common adverse reactions for montelukast (incidence ≥5% and greater than placebo) include upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, and otitis.
- The most common adverse reaction for zafirlukast for patients ≥12 years of age (incidence ≥5% and greater than placebo) is headache. For children aged five to 11 years, the most common adverse reactions (incidence ≥2% and higher than placebo) include headache and abdominal pain.
- The most common adverse reactions for zileuton (incidence ≥5% and greater than placebo) include headache, dyspepsia, unspecified pain, and nausea. For extended-release zileuton, the most common adverse reactions (≥5% and more than placebo) include sinusitis, nausea, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Generic Name	Dosage Form: Strength	Usual Adult Dose	Pediatric Dose	Administration Considerations
Montelukast	Chewable tablet: 4 mg 5 mg Oral granules: 4 mg Tablet: 10 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: 10 mg once daily in the evening <u>Prevention of exercise-induced bronchoconstriction:</u> Tablet: 10 mg at least two hours before exercise; additional doses should not be administered within 24 hours <u>Relief of symptoms of perennial and seasonal allergic rhinitis:</u> Tablet: 10 mg daily at any time of day	<u>Prophylaxis and chronic treatment of asthma:</u> Chewable tablet: six to 14 years of age, 5 mg once daily in the evening; two to five years of age, 4 mg once daily in the evening Oral granules: 12 months to five years of age, 4 mg once daily in the evening Tablet: 15 years of age and older, 10 mg once daily in the evening <u>Prevention of exercise-induced bronchoconstriction:</u> Chewable tablet: six to 14 years of age: 5 mg at least two hours before exercise	May be taken with or without food. Oral granules may be given directly in the mouth or mixed with baby formula, breast milk, or soft foods (applesauce, carrots, rice, or ice cream). Contents of the packet must be administered within 15 minutes after opening the packet.

Generic Name	Dosage Form: Strength	Usual Adult Dose	Pediatric Dose	Administration Considerations
			Tablet: 15 years of age and older, 10 mg at least two hours before exercise <u>Relief of symptoms of perennial and seasonal allergic rhinitis:</u> Chewable tablet: two to five years of age, 4 mg once daily; six to 14 years of age, 5 mg once daily Oral granules: six months to five years of age (perennial) or two to five years of age (seasonal allergic rhinitis), 4 mg once daily Tablet: 15 years of age and older, 10 mg once daily	
Zafirlukast	Tablet: 10 mg 20 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: 20 mg twice daily	<u>Prophylaxis and chronic treatment of asthma:</u> Tablet: five to 11 years of age, 10 mg twice daily; 12 years of age and older, 20 mg twice daily	Should be taken within one hour before or two hours after meals
Zileuton	Extended release tablet: 600 mg Tablet: 600 mg	<u>Prophylaxis and chronic treatment of asthma:</u> Extended release tablet: 1,200 mg twice daily Tablet: 600 mg four times a day	<u>Prophylaxis and chronic treatment of asthma:</u> Extended release tablet: 12 years of age and older, 1,200 mg twice daily Tablet: 12 years of age and older, 600 mg four times a day	Extended-release tablet: Should be taken within one hour after morning and evening meals. Tablet: Should be taken with meals and at bedtime.

SPECIAL POPULATIONS

Table 4. Special Populations

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Montelukast	No dosage adjustment required in the elderly population.	Approved for use in children 12 months of age and older for asthma, six years of age and older for exercise induced bronchoconstric-tion, two years of age and older for seasonal allergic rhinitis, and six months of age	No dosage adjustment required.	No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. Studies have not been conducted in patient with severe hepatic disease.	Pregnancy Category B Unknown whether excreted in breast milk; use caution.

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		and older for perennial allergic rhinitis.			
Zafirlukast	No dosage adjustment required in the elderly population.	Approved for use in children five years of age and older.	No dosage adjustment required.	Contraindicated in patients with hepatic impairment, including cirrhosis.	Pregnancy Category B Excreted in breast milk; do not administer to nursing mothers.
Zileuton	No dosage adjustment required in the elderly population.	Safety and efficacy in pediatric patients under 12 years of age have not been established; use is not recommended.	No dosage adjustment required.	Contraindicated in patients with active liver disease and in patients with transaminase elevations greater than or equal to three times the upper limit of normal.	Pregnancy Category C Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The leukotriene modifiers consist of two categories of agents: the leukotriene receptor antagonists (montelukast and zafirlukast) and the 5-lipoxygenase inhibitor (zileuton). All leukotriene modifiers are FDA-approved for the chronic treatment and prophylaxis of asthma. Montelukast is also indicated for prophylaxis of exercise-induced bronchoconstriction as well as for the treatment of symptoms of both seasonal and perennial allergic rhinitis.
- Current treatment guidelines recommend the use of leukotriene modifiers as a treatment alternative to low-dose ICSs in patients with mild persistent asthma. In mild asthma, adding a leukotriene receptor antagonist may allow an ICS dose to be stepped down, as well. These agents can also be considered as alternative adjunctive therapy in patients not achieving adequate symptom control with an ICS as monotherapy or in combination with a LABA. Either leukotriene receptor antagonist is preferred over zileuton due to the latter's limited efficacy data and the need for liver function monitoring (GINA, 2017; NHLBI, 2007). Guidelines position intranasal corticosteroids as first-line treatments for the management of allergic rhinitis, and note that the leukotriene modifiers can be considered as second-line agents along with antihistamines (Wallace et al, 2008; Brozek et al, 2010). A guideline for the treatment of exercise-induced bronchoconstriction recommends that β_2-agonists are the most effective therapy for the prophylaxis and relief of bronchoconstriction, while leukotriene receptor antagonists may also be used as prophylaxis but have no role on reversal of airway obstruction (Parsons et al, 2013; Weiler et al, 2016).
- In placebo-controlled trials, the leukotriene modifiers demonstrated efficacy in most aspects of asthma control. However, when compared to other long-term control medications, such as ICSs and LABAs, the leukotriene modifiers were unable to demonstrate equivalence or significant advantages in clinical outcomes. In patients with allergic rhinitis, montelukast has been shown to be more effective than placebo and has demonstrated comparable efficacy to the second-generation antihistamines; however, it was shown to be less effective than intranasal corticosteroids. Montelukast has also been shown to be more effective than placebo in preventing exercise-induced bronchoconstriction (Wasfi et al, 2011). Although one small, open-label trial suggests that extended-release zileuton has better therapeutic efficacy for the treatment of asthma in comparison to montelukast, comparative trial data is insufficient to draw any definitive conclusions (Kubavat et al, 2013).

- In regards to safety, postmarking data show that both zafirlukast and zileuton appear to have a higher risk of hepatotoxicity than montelukast. In addition, when compared to the other two agents, montelukast has the advantages of fewer drug interactions and more data supporting its use in children and infants as young as six months of age.

REFERENCES

- ACCOLATE prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. November 2013.
- Baena-Cagnani CE, Berger WE, DuBuske LM, et al. Comparative effects of desloratadine vs montelukast on asthma symptoms and use of beta$_2$ agonists in patients with seasonal allergic rhinitis and asthma. Int Arch Allergy Immunol. 2003 Apr;130(4):307-13.
- Bjermer L, Bisgaard H, Bousquet J, et al. Montelukast and fluticasone compared to salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomized comparative trial. BMJ. 2003 Oct;327(7420):891.
- Bozek A, Warkocka-Szoltysek B, Filipowska-Gronska A, et al. Montelukast as an add-on therapy to inhaled corticosteroids in the treatment of severe asthma in elderly patients. J Asthma. 2012 Jun;49(5):530-4.
- Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010 Sep;126(3):466-76.
- Busse W, Nelson H, Wolfe J, et al. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol. 1999 Jun;103(6):1075-80.
- Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared to montelukast for first-line treatment of persistent asthma: a randomized clinical trial. J Allergy Clin Immunol. 2001 Mar;107(3):461-8.
- Calhoun WJ, Nelson HS, Nathan RA, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short acting beta$_2$ agonists alone. Am J Respir Crit Care Med. 2001 Sep;164(5):759-63.
- Chauhan BF, Ben Salah R, Ducharme FM. Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma. Cochrane Database of Systematic Reviews. 2013, Issue 10. Art. No.: CD009585. doi:10.1002/14651858.CD009585.pub2.
- Cingi C, Ozlugedik S. Effects of montelukast on quality of life in patients with persistent allergic rhinitis. Otolaryngol Head Neck Surg. 2010 May;142(5):654-8.
- Chen CF, LV Y, Zhang HP, Wang G. Does zafirlukast reduce future risk of asthma exacerbations in adults? Systematic review and meta-analysis. Multidisciplinary Respir Med. 2014;9(1):30. doi:10.1186/2049-6958-9-30.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 15, 2017.
- Ducharme F, Lasserson T, Cates C. Long-acting beta-2 agonists vs anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev. 2006 Oct;(4):CD003137.
- Esteitie R, deTineo M, Naclerio R, et al. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2010 Aug;105(2):155-61.
- Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001 Aug;120(2):423-30.
- Garcia ML, Wahn U, Gilles L, et al. Montelukast compared to fluticasone for control of asthma among six to 14-year-old patients with mild asthma: the MOSAIC study. Pediatrics. 2005 Aug;116(2):360-9.
- Glacy J, Putnam K, Godfrey S, et al. Treatments for seasonal allergic rhinitis. comparative effectiveness review no. 120. (prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under contract no. 290-2007-10058-I.) AHRQ Publication No. 13-EHC098-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed April 25, 2017.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2017. Available at: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed April 15, 2017.
- Israel E, Cohn L, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. JAMA. 1996 Mar 27;275(12):931-6.
- Israel E, Rubin P, Kemp J, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. Ann Intern Med. 1993;119(11):1059-66.
- Knorr B, Matz J, Bernstein J, et al. Montelukast for chronic asthma in six to14 year old children: a randomized, double blind trial. JAMA. 1998 Apr;279(15):1181-6.
- Kubavat AH, Khippal N, Tak S, et al. A randomized, comparative, multicenter clinical trial to assess the efficacy and safety of zileuton extended-release-tablets with montelukast sodium tablets in patients suffering from chronic persistent asthma. American Journal of Therapeutics. 2013;20:154-62.
- Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010 Mar 18;362(11):975-85.
- Li AM, Abdullah VJ, Tsen CS, et al. Leukotriene receptor antagonist in the treatment of childhood allergic rhinitis- a randomized placebo-controlled study. Pediatr Pulmonol. 2009 Nov;44(11):1085-92.
- Maspero J, Guerra F, Cuevas F, et al. Efficacy and tolerability of salmeterol/fluticasone propionate vs montelukast in childhood asthma: a prospective, randomized, double-blind, double-dummy, parallel-group study. Clin Ther. 2008 Aug;30(8):1492-504.
- Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol. 2000 May;105(5):917-22.
- Mucha SM, deTineo M, Naclerio RM, et al. Comparison of montelukast and pseudoephedrine in the treatment of allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2006 Feb;132(2):164-72.
- National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma full report 2007. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed April 25, 2017.

- Nelson H, Kemp J, Berger W, et al. Efficacy of zileuton controlled-release tablets administered twice daily in the treatment of moderate persistent asthma: a three-month randomized controlled study. Ann Allergy Asthma Immunol. 2007 Aug;99(2):178-84.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US) website; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 21, 2017.
- Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016-27.
- Price DB, Hernandez D, Magyar P, et al. Randomized controlled trial of montelukast plus inhaled budesonide vs double dose inhaled budesonide in adult patients with asthma. Thorax. 2003 Mar;58(3):211-6.
- Pullerits T, Praks L, Ristioja V, Lötvall J. Comparison of nasal glucocorticoid, antileukotriene, and combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2002 Jun;109(6):949-55.
- Reiss T, Chervinsky P, Dockhorn R, et al. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double blind trial. Arch Intern Med. 1998 Jun; 158 (11):1213-20.
- Saengpanich S, deTineo M, Naclerio RM, et al. Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2003 May;129(5):557-62.
- Seidman MD, Gurgel RK, Lin ST, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):SI-S43.
- SINGULAIR prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. December 2016.
- Skloot GS, Busse PJ, Braman SS, et al. An official American Thoracic Society workshop report: evaluation and management of asthma in the elderly. Ann Am Thorac Soc. 2016;13(11):2064-2077.
- Snellman L, Adams W, Anderson G, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Respiratory Illness in Children and Adults. Updated January 2013. Available at: https://www.icsi.org/_asset/1wp8x2/RespIllness.pdf. Accessed April 25, 2017.
- Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of three controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial. J Allergy Clin Immunol. 2007 Jan;119(1):64-72.
- Suissa S, Dennis R, Ernst P, et al. Effectiveness of the leukotriene receptor antagonist zafirlukast for mild-to-moderate asthma: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1997 Feb;126(3):177-83.
- Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005 Feb;115(2):233-42.
- Virchow J, Mehta A, Ljungblad L, Mitfesse H, MONICA study group. Add-on montelukast in inadequately controlled asthma patients in a six-month open-label study: The MONtelukast in Chronic Asthma (MONICA) study. Respir Med. 2010(a) May;104(5):644-51.
- Virchow J, Mehta A, Ljungblad L, Mitfessel H. A subgroup analysis of the MONICA study: a 12-month, open-label study of add-on montelukast treatment in asthma patients. J Asthma. 2010(b) Nov;47(9):986-93.
- Visitsunthorn N, Chirdjirapong V, Santadilog S, et al. The effect of montelukast on bronchial hyperreactivity and lung function in asthmatic children aged six to13 years. Asian Pac J Allergy Immunol. 2011 Jun;29(2):127-33.
- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84.
- Wasfi YS, Kemp JP, Villarán C, et al. Onset and duration of attenuation of exercise-induced bronchoconstriction in children by single-dose of montelukast. Allergy Asthma Proc. 2011 Nov-Dec;32(6):453-9.
- Wei C. The efficacy and safety of H1-antihistamine versus montelukast for allergic rhinitis: A systematic review and meta-analysis. Biomed Pharmacother. 2016;83:989-997.
- Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. J Allergy Clin Immunol. 2016;138(5):1292-1295.
- Wenzel S, Busse W, Calhoun W, et al. The safety and efficacy of zileuton controlled-release tablets as adjunctive therapy to usual care in the treatment of moderate persistent asthma: a six-month randomized controlled study. J Asthma. 2007 May;44(4):305-10.
- Wilson EC, Price D, Musgrave SD, et al. Cost effectiveness of leukotriene receptor antagonists vs long-acting beta-2 agonists as add-on therapy to inhaled corticosteroids for asthma: a pragmatic trial. Pharmacoeconomics. 2010(b);28(7):597-608.
- Wilson EC, Sims EJ, Musgrave SD, et al. Cost effectiveness of leukotriene receptor antagonists vs inhaled corticosteroids for initial asthma controller therapy: a pragmatic trial. Pharmacoeconomics. 2010(a);28(7):585-95.
- Yildirim Z, Ozlu T, Bulbul Y, Bayram H. Addition of montelukast vs double dose of inhaled budesonide in moderate persistent asthma. Respirology. 2004 Jun;9(2):243-8.
- Zeiger RS, Szefler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol. 2006 Jan;117(1):45-52.
- ZYFLO prescribing information. Chiesi USA Inc. Cary, NC. June 2014.
- ZYFLO CR prescribing information. Chiesi USA Inc. Cary, NC. January 2017.

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Therapeutic Class Overview
Beta Agonist and Corticosteroid Combinations

INTRODUCTION

- Respiratory β_2-agonist/inhaled corticosteroid (ICS) combinations are used to treat asthma and/or chronic obstructive pulmonary disease (COPD). The specific indications vary based on the product and the strength. All β2-agonist/ICS combinations are brand-name only at this time, with the exception of AIRDUO RESPICLICK (fluticasone propionate/salmeterol), for which an authorized generic is marketed.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (National Heart, Lung, and Blood Institute [NHLBI], 2014).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (NHLBI, 2014).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (NHLBI, 2007).
- Long-term control medications for asthma include the following (NHLBI, 2007):
    - Corticosteroids (ICSs for long-term control, short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (ie, omalizumab)
    - Leukotriene modulators
    - Long-acting β-agonists (LABAs)
    - Methylxanthines (ie, theophylline)
- Quick-relief medications for asthma include the following (NHLBI, 2007):
    - Short-acting β-agonists (SABAs) (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (NHLBI, 2007)
- In recent years, additional medications have been made available for select subsets of patients with asthma, including mepolizumab and reslizumab for the management of severe asthma with an eosinophilic phenotype (Prescribing information: CINQAIR, 2016; NUCALA, 2017). Additionally, tiotropium, long used for COPD, has been FDA approved for the treatment of asthma (SPIRIVA RESPIMAT prescribing information, 2017).
- ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. Alternative long-term control medications include LABAs, leukotriene modifiers, mast-cell stabilizers, and methylxanthines (theophylline). The LABAs should not be used as monotherapy for the management of asthma; however, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. Omalizumab, mepolizumab, or reslizumab may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while mepolizumab or reslizumab are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (NHLBI, 2007; Global Initiative for Asthma [GINA], 2017).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of

COPD include dyspnea, cough, and sputum production (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2017).

- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention, 2016). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (GOLD, 2017).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (GOLD, 2017).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (GOLD, 2017).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (GOLD, 2017).
- Pharmacologic options for COPD treatment comprise several classes, including β_2-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with ICSs), and the phosphodiesterase (PDE)-4 inhibitor roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (GOLD, 2017).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (GOLD, 2017).
- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. However, use of a long-acting muscarinic antagonist (LAMA)/LABA combination has been shown to decrease exacerbations more than an ICS/LABA combination, and regular treatment with an ICS increases the risk of pneumonia (GOLD, 2017).
- β_2-agonists and ICSs can be administered separately or in combination products. Asthma patients with milder symptoms who do not require daily use of a LABA may benefit from separate administration of an ICS and use of a SABA for breakthrough symptoms. For patients requiring daily use of both an ICS and a LABA, combination products can provide a convenient option. In addition, it is important to note that for asthma treatment, a LABA should not be given without concomitant use of a long-term asthma control medication, such as an ICS. For patients with asthma who require the addition of a LABA to an ICS, a fixed-dose combination product can help ensure adherence with both drugs.
- This review includes the combination ICS/LABA combinations. The products in this category are shown in Table 1.
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ADVAIR DISKUS & ADVAIR HFA (fluticasone propionate/salmeterol)	-
AIRDUO RESPICLICK (fluticasone propionate/salmeterol)	✔ *
BREO ELLIPTA (fluticasone furoate/vilanterol)	-
DULERA (mometasone furoate/formoterol fumarate dihydrate)	-
SYMBICORT (budesonide/formoterol fumarate dihydrate)	-

*Authorized generic

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ADVAIR DISKUS	ADVAIR HFA	AIRDUO RESPICLICK	BREO ELLIPTA	DULERA	SYMBICORT
Treatment of asthma	✔ (age ≥4 years)	✔ (age ≥12 years)	✔ (age ≥12 years)	✔ (age ≥18 years)	✔ (age ≥12 years)	✔ (age ≥6 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		

(Prescribing information: ADVAIR HFA, 2017; ADVAIR DISKUS, 2017; AIRDUO RESPICLICK, 2017; BREO ELLIPTA, 2017; DULERA, 2016; SYMBICORT, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Comparisons to Placebo, Monotherapy, Combined use of Individual Components, Varied Treatments, or Usual Care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (Bateman et al, 2001; Bateman et al, 2004; Bateman et al, 2006; Bateman et al, 2014; Berger et al, 2010; Bernstein et al, 2015; Bleecker et al, 2014; Calverley et al, 2003; Corren et al, 2007; Eid et al, 2010; Gappa et al, 2009; Hanania et al, 2003; Jenkins et al, 2006; Kerwin et al, 2009; Kerwin et al, 2013; Kuna et al, 2006; Lalloo et al, 2003; Lundback et al, 2006; Martinez et al, 2013; Meltzer et al, 2012; Morice et al, 2007; Murphy et al, 2008; Nelson et al, 2003b; Nathan et al, 2006; Noonan et al, 2006; O'Byrne et al, 2014; Pearlman et al, 2004; Pohl et al, 2006; Rennard et al, 2009; Sharafkaneh et al, 2012; Tal et al, 2002; Tashkin et al, 2008; Vaessen-Verberne et al, 2010; Vestbo et al, 2005; Weinstein et al, 2010; Zangrilli et al, 2011). Results for reducing COPD exacerbations have been inconsistent. One head-to-head trial in patients with a recent exacerbation of COPD demonstrated no significant difference between fluticasone propionate/salmeterol 250/50 mcg twice daily and salmeterol 50 mcg twice daily in severe or moderate/severe COPD exacerbations (Ohar et al, 2014). Pooled results of two trials comparing varying doses of fluticasone furoate/vilanterol with vilanterol 25 mcg daily demonstrated a reduction in moderate/severe COPD exacerbations with fluticasone furoate/vilanterol compared to vilanterol alone (Dransfield et al, 2013).
- Additionally, there is similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (Chapman et al, 1999; Jenkins et al, 2006; Marceau et al, 2006; Noonan et al, 2006; Nelson et al, 2003a; Perrin et al, 2010; Rosenhall et al, 2002; Zangrilli et al, 2011).
- AIRDUO RESPICLICK (fluticasone propionate/salmeterol) was approved by the FDA in April 2017 as a new combination delivered via the RespiClick device based on a clinical program consisting of three phase 2 placebo-controlled dose-ranging trials, two phase 3 efficacy trials, and a 26-week long-term safety trial in patients with persistent asthma (FDA medical review, 2017; Mansfield et al, 2016; Miller et al, 2016; Raphael et al, 2016; Raphael et al, 2017; Sher et al, 2016; Sher et al, 2017).
    - Two 12-week dose-ranging trials (total N=1,262) determined that fluticasone propionate 100 mcg delivered via the RespiClick resulted in a similar FEV_1 improvement compared with the marketed mid-dose fluticasone propionate (FLOVENT DISKUS) 100 mcg (295 mL vs. 234 mL, respectively); this supported the proposed fluticasone propionate low (50 mcg) and mid (100 mcg) doses delivered via the RespiClick (FDA medical review, 2017).
    - The FEV_1 change from baseline to week 12 for fluticasone propionate (FLOVENT DISKUS) 250 mcg was between the fluticasone propionate 100 mcg and 200 mcg RespiClick doses, which supported the proposed fluticasone propionate high (200 mcg) dose delivered via the RespiClick (FDA medical review, 2017).

- A crossover study (N=72) determined the FEV_1 area under the curve 12 hours post-dose (FEV_1 AUC_{0-12}) of the fluticasone propionate/salmeterol (ADVAIR DISKUS) 100/50 mcg dose was most comparable to that of the fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 100/12.5 mcg dose (245 vs. 249 mL, respectively; P=0.8503), which supported the proposed fixed 12.5 mcg dose of salmeterol delivered via the RespiClick (Miller et al, 2016).
- Two 12-week studies (N=1,445) evaluated the efficacy of fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 50/12.5 mcg, 100/12.5 mcg, and 200/12.5 mcg vs. the corresponding fluticasone propionate monotherapy doses delivered via the RespiClick device and placebo (FDA medical review, 2017; Raphael et al, 2016; Raphael et al, 2017; Sher et al, 2016; Sher et al, 2017).
  - In all studies, treatment with fluticasone propionate/salmeterol (AIRDUO RESPICLICK) significantly increased pulmonary function vs. placebo, and was significantly superior in improving FEV_1 vs. fluticasone propionate monotherapy delivered via the RespiClick, with a similar safety profile.
- Results from the long-term safety trial (N=674) demonstrated asthma exacerbation as the most frequently reported serious adverse event (4% overall), while treatment-related adverse events occurred more frequently with the high-dose fluticasone propionate/salmeterol (ADVAIR DISKUS) 500/50 mcg and fluticasone propionate (FLOVENT HFA) 220 mcg doses vs. fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 100/12.5 mcg and 200/12.5 mcg doses and fluticasone propionate 100 mcg and 200 mcg delivered via the RespiClick due to a higher incidence of oral candidiasis (11 and 12%, respectively, vs. 0 to 5%) (FDA medical review, 2017; Mansfield et al, 2016).

- A large, double-blind, randomized trial (N=6,112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a three-year period in patients with COPD. The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; P=0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; P=0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo (Calverley et al, 2007).
- A large, double-blind, randomized trial (SUMMIT; N=16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (Vestbo et al, 2016a). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; P=0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; P=0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; P=0.655]). Composite cardiovascular events were also similar in the four groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N=2,799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (Vestbo et al, 2016b). Enrolled patients had COPD, had had one or more exacerbations in the previous three years, and were taking regular maintenance inhaler therapy (one or more long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; P=0.02). Serious adverse events, including pneumonia, were similar between the two groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD. This analysis demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo. Looking at the number of patients who experienced one or more exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol (200/10 mcg strength) vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99) (Nannini et al, 2013).

- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD. This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01) (Nannini et al, 2012).
- A meta-analysis of 7 trials evaluated the use of once-daily fluticasone furoate/vilanterol for adolescents and adults with symptomatic asthma compared to ICS monotherapy or twice-daily ICS/LABA formulations. All were double-blind, randomized trials and the duration ranged from 12 to 78 weeks (median, 24 weeks). The following results relating to fluticasone furoate/vilanterol compared to ICS monotherapy were demonstrated (Rodrigo et al, 2016):
    - Three trials in 3,667 patients comparing fluticasone furoate/vilanterol to fluticasone furoate 100 mcg demonstrated a significant increase in trough forced expiratory volume in one second (FEV_1) (mean difference [MD], 90 mL; P<0.001) and in morning and evening peak expiratory flow (PEF) (MD, 20.1 L/min; P<0.001 and 18.9 L/min; P=0.003, respectively). There was also a significant improvement in the proportion of patients with ≥1 severe asthma exacerbation.
    - Three trials in 1,398 patients comparing fluticasone furoate/vilanterol to fluticasone propionate 500 mcg twice daily demonstrated a significant increase in weighted FEV_1 (MD, 140 mL; P=0.002) and in morning and evening PEF (MD, 32.6 L/min; P<0.001 and 25.7 L/min; P<0.001, respectively). There were also significant improvements in the proportion of patients with ≥1 severe asthma exacerbation.
- A meta-analysis of 14 trials (total N=6,641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (Dwan et al, 2016). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (MD, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions cannot be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several recently published, large studies focused primarily on safety endpoints, with efficacy endpoints as secondary. The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering some reassurance for the safety of these agents (Peters et al, 2016; Stempel et al, 2016a; Stempel et al, 2016b).
    - A recent randomized, double-blind study (AUSTRI; N=11,679) enrolled adults and adolescents (age ≥12 years) with persistent asthma and a history of exacerbation within the previous year (Stempel et al, 2016a). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
        - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be noninferior to fluticasone for this endpoint. There were no asthma-related deaths.
        - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least one severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone group (HR, 0.79; 95% CI, 0.70 to 0.89; P<0.001).

- A similarly designed trial (VESTRI; N=6,208) enrolled pediatric patients 4 to 11 years of age (Stempel et al, 2016b). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone alone 100 mcg or 250 mcg twice daily for 26 weeks.
  - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone (P=0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
  - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone group (HR, 0.86; 95% CI, 0.73 to 1.01).
- An additional randomized, double-blind trial (N=11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥12 years of age (Peters et al, 2016). Enrolled patients were receiving daily asthma medication and had had at least one exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (two actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (two actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
  - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated noninferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
  - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).

<u>Comparisons Between Different ICS/LABA Combinations</u>

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in PEF five minutes after the morning dose. However, the mean morning FEV_1 improved more with budesonide/formoterol at five minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol (Partridge et al, 2009).
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr). However, two of these three trials did not demonstrate a significant difference on this endpoint (Dransfield et al, 2014). An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (Agusti et al, 2014).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma:
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (Dahl et al, 2006; Fitzgerald et al, 2005; Price et al, 2007); some

showed benefits for budesonide/formoterol (Aalbers et al, 2004; Kuna et al, 2007; Palmqvist et al, 2001), and another showed no significant differences between the two products (Busse et al, 2008).
  - A meta-analysis of five trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or PEF (Lasserson et al, 2011).
  - A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 AUC_{0-12}. Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups (Bernstein et al, 2011).
  - A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥12% and ≥200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1(Woodcock et al, 2013).

<u>ICS/LABA Compared to Leukotriene Modifiers and Leukotriene Modifier Combination Regimens for Asthma</u>
- Several head-to-head trials have demonstrated the benefits of fluticasone propionate/salmeterol treatment compared to regimens containing leukotriene modifiers. In varied patient populations, fluticasone propionate/salmeterol was shown to be superior to montelukast and superior to a combination of fluticasone and montelukast for endpoints including PEF, FEV_1, improvement in asthma symptoms, and reduction in exacerbations (Calhoun et al, 2001; Maspero et al, 2008; Ringdal et al, 2003).
- Results from a meta-analysis of studies comparing the leukotriene modifiers montelukast and zafirlukast to fluticasone propionate/salmeterol and other ICS/LABA combinations found that outcomes were consistent with those from head-to-head trials. Notably, the risk of having an exacerbation requiring systemic corticosteroids was modestly lower with the use of a LABA plus an ICS compared to a leukotriene modifier plus an ICS (risk ratio, 0.87; 95% CI, 0.76 to 0.99) (Chauhan et al, 2014).

<u>ICS/LABA Compared to Tiotropium or in Combination with Tiotropium for COPD</u>
- A double-blind, double-dummy, two-year trial (N=1,323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD. This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms (Wedzicha et al, 2008).
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (Hanania et al, 2012; Welte et al, 2009). One double-blind trial (Welte et al, 2009) also demonstrated a reduction in the risk of severe COPD exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (Aaron et al, 2007; Hanania et al, 2012; Karner et al, 2011).

<u>ICS/LABA Compared to LAMA/LABA Combinations</u>
- Several LAMA/LABA combinations have recently been made available, and there are some data to support their benefits compared to ICS/LABA combinations in selected patients with COPD. One large, randomized, double-blind, 52-week trial (FLAME; N=3,362) compared indacaterol/glycopyrronium 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Wedzicha et al, 2016). (Indacaterol/glycopyrrolate has been FDA approved, but the dosing regimen in the U.S. product differs from that which was evaluated in this study.) The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrronium group than in the fluticasone propionate/salmeterol group (3.59 vs. 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003). Lung function was also improved to a greater extent with indacaterol/glycopyrronium, with a difference in trough FEV_1 of 62 mL between

groups (P<0.001). A similar but smaller 26-week study (LANTERN; N=744) enrolling a predominantly Chinese population with not more than one exacerbation in the previous year demonstrated similar results (Zhong et al, 2015).

Off-label Use

- Some studies have evaluated ICS/LABA combinations for off-label uses. For example, the combination mometasone furoate/formoterol fumarate dihydrate (DULERA) is FDA-approved for the treatment of asthma, but has also been evaluated and demonstrated to be effective for the treatment of COPD (Doherty et al, 2012; Tashkin et al, 2012).
- Several clinical trials have evaluated SYMBICORT Maintenance And Reliever Therapy (SMART) dosing, a simplified management approach for asthma in which budesonide/formoterol is given as a maintenance inhaler, and additional doses are used for relief of symptoms (Atienza et al, 2013; Bousquet et al, 2007; Kew et al, 2013; Kuna et al, 2007; Quirce et al, 2011; Rabe et al, 2006; Riemersma et al, 2012; Scicchitano et al, 2004; Soes-Petersen et al, 2011; Vogelmeier et al, 2012). However, this approach to dosing is not FDA approved for budesonide/formoterol, and the prescribing information warns against excessive use of more than two inhalations twice daily. Budesonide/formoterol has also shown some effectiveness as an on-demand (rather than maintenance) treatment in patients with mild asthma and exercise-induced bronchoconstriction; however, this use is also not FDA approved (Lazarinis et al, 2014).
- The focus of this review is limited to FDA-approved uses for the ICS/LABA inhalers.

CLINICAL GUIDELINES

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (NHLBI, 2007).
    - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
    - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, omalizumab, mepolizumab) (GINA, 2017). The Institute for Clinical Systems Improvement (ICSI) endorsed the updated GINA guideline (ICSI, 2016).
- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (GINA, 2017; NHLBI, 2007).
- The 2017 GOLD guidelines underwent a significant update from prior guideline versions. The guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (GOLD, 2017):
    - Inhaled bronchodilators are recommended over oral bronchodilators.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
    - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two.
    - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
    - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).

- Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
- Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
- Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
- Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT <10	mMRC ≥2 CAT ≥10
≥2 (or ≥1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guideline states that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (Criner et al, 2015).

SAFETY SUMMARY

Contraindications:

- β_2-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- β_2-agonist/ICS combinations are generally contraindicated in patients with hypersensitivity to any ingredients in the formulation. ADVAIR DISKUS, AIRDUO RESPICLICK, and BREO ELLIPTA are specifically contraindicated in patients with a severe hypersensitivity to milk proteins.

Key Warnings and Precautions:

- All medications that include a LABA have a boxed warning about the increased risk of asthma-related death. The increased risk was observed in a trial using salmeterol, but is considered a class effect of LABAs. Currently available data are inadequate to determine whether concurrent use of ICSs or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. When treating patients with asthma, a combination ICS/β_2 agonist should only be used for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.
- Other key warnings and precautions include:
  - significant cardiovascular effects and fatalities with excessive use of β_2-agonists
  - cardiovascular and/or central nervous system effects from β-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - paradoxical bronchospasm

- hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
- the need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
- lower respiratory tract infections/pneumonia
- local infections of the mouth and pharynx with *Candida albicans*
- reduced growth velocity in pediatric patients
- the potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
- the potential for developing glaucoma, increased intraocular pressure, or cataracts

- It is also important to note that ICS/β_2-agonist combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.

Adverse Events

- Commonly reported adverse events (≥5% for at least one medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Comments
ADVAIR DISKUS (fluticasone propionate/ salmeterol)	Inhalation powder: 100/50 mcg, 250/50 mcg, 500/50 mcg	Asthma: adults and children ≥ 12 years of age: Initial, one inhalation twice a day; maximum, 500/50 mcg twice a day Asthma: children 4 to 11 years of age: One 100/50 mcg inhalation twice a day (for patients not controlled on an ICS) Maintenance treatment of airflow obstruction in patients with COPD*: One 250/50 mcg inhalation twice a day	Patient should rinse mouth with water without swallowing after inhalation. Starting dose should be based upon the patient's asthma severity. Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
ADVAIR HFA (fluticasone propionate/ salmeterol)	Metered dose aerosol inhaler: 45/21 mcg, 115/21 mcg, 230/21 mcg	Asthma: adults and children ≥ 12 years of age: Initial, two inhalations twice a day; maximum, two 230/21 mcg inhalations twice a day	Patient should rinse mouth with water without swallowing after inhalation. Starting dose should be based upon the patient's asthma severity. Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
AIRDUO RESPICLICK (fluticasone propionate/ salmeterol)	Inhalation powder: 55/14 mcg, 113/14 mcg, 232/14 mcg	Asthma: adults and children ≥ 12 years of age: One 55/14 mcg, 113/14 mcg, or 232/14 mcg inhalation twice a day	Patient should rinse mouth with water without swallowing after inhalation. Starting dose should be based upon prior asthma therapy and disease severity. Dose may be increased if patient does not adequately respond after 2 weeks of therapy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Comments
BREO ELLIPTA (fluticasone furoate/ vilanterol)	Inhalation powder: 100/25 mcg, 200/25 mcg	COPD: One 100/25 mcg inhalation daily Asthma: patients ≥ 18 years of age: Initial, one 100/25 mcg or one 200/25 mcg inhalation daily; maximum, one 200/25 mcg inhalation once daily	Patient should rinse mouth with water without swallowing after inhalation. Starting dose should be based upon the patient's asthma severity. For patients who do not respond adequately to 100/25 mcg, increasing the dose to 200/25 mcg may provide additional improvement in asthma control.
DULERA (mometasone furoate/ formoterol fumarate dihydrate)	Metered dose aerosol inhaler: 100/5 mcg, 200/5 mcg	Asthma: adults and children ≥12 years of age: Initial, two 100/5 mcg inhalations twice a day if previous therapy with medium dose ICS, or two 200/5 mcg inhalations twice a day if previous therapy with high dose ICS; maintenance, two inhalations twice a day; maximum, two 200/5 mcg inhalations twice a day	Inhaler should be shaken well before each use. Patient should rinse mouth with water without swallowing after inhalation. Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
SYMBICORT (budesonide/ formoterol fumarate dihydrate)	Metered dose aerosol inhaler: 80/4.5 mcg, 160/4.5 mcg	Asthma: adults and children ≥12 years of age: Initial, two inhalations twice a day; Maximum; two 160/4.5 mcg inhalations twice a day. Starting dose should be based upon the patient's asthma severity; Dose may be increased if patient does not adequately respond after one to 2 weeks of therapy. Asthma: children 6 to 11 years of age: Two 80/4.5 mcg inhalations twice a day Maintenance treatment of airflow obstruction in patients with COPD†: Two 160/4.5 mcg inhalations twice a day	Patient should rinse mouth with water without swallowing after inhalation.

*ADVAIR 250/50 mcg is the only strength FDA-approved for this indication.
†SYMBICORT 160/4.5 mcg is the only strength FDA-approved for this indication.

CONCLUSION

- The combination ICS/LABA products are all FDA-approved for the treatment of asthma, and some are also indicated for the treatment of COPD. In some cases, the specific indications vary by the strength of the inhaler. FDA approval also varies by age for the treatment of children with asthma; ADVAIR DISKUS is the only ICS/LABA product approved for treating asthma in children aged 4 to 11 years, while SYMBICORT is approved for treating asthma in children aged 6 to 11 years.
- The combination ICS/LABA products are not available generically, with the exception of the AIRDUO RESPICLICK authorized generic. The individual components of the inhalers are also not available generically.
- Trials have demonstrated that the combination products are superior to the individual separate components given as monotherapy for the treatment of both asthma and COPD. Data from comparative trials do not consistently demonstrate superiority for any one combination ICS/LABA over another.

- For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS as monotherapy (GINA, 2017; ICSI, 2016; NHLBI, 2007).
- For the treatment of COPD, guidelines from the Global Initiative for Chronic Obstructive Lung Disease recommend the use of ICS/LABA products as an option for some patients at higher risk of exacerbations; however, bronchodilators (one or two, depending on symptom severity) *without* an ICS are recommended as first-line treatments for all COPD patients (GOLD, 2017).
- None of the current asthma or COPD treatment guidelines recommend the use of one combination ICS/LABA product over another (Criner et al, 2015; GINA, 2017; GOLD, 2017; NHLBI, 2007).
- A practical benefit of combination ICS/LABAs is that their use ensures that patients are not using a LABA without concomitant ICS. This is particularly important for patients with asthma, because LABAs increase the risk of asthma-related death and should only be used to treat asthma in patients also taking a long-term asthma controller, such as an ICS. Combination products also provide added patient convenience. However, a disadvantage to combination therapy is that doses of the ICS cannot be titrated as easily as when the ICS is administered separately.

Table 6. Advantages and Disadvantages of Combination ICS/LABAs

Drug	Advantages	Disadvantages
ADVAIR DISKUS and ADVAIR HFA (fluticasone propionate and salmeterol)	• Available as an inhalation powder (ADVAIR DISKUS) in three strengths and as an inhalation aerosol (ADVAIR HFA) in three strengths • FDA-approved to treat asthma (all formulations/strengths) and COPD (ADVAIR DISKUS 250/50 mcg) • Indicated for maintenance treatment of airflow obstruction and for reducing COPD exacerbations (ADVAIR DISKUS 250/50 mcg) • ADVAIR DISKUS is FDA-approved to treat asthma in children aged 4 years and older • Established therapy (initial FDA approval in 2000)	• Administered twice daily • ADVAIR HFA is FDA-approved to treat asthma in patients aged ≥12 years; not in young children
AIRDUO RESPICLICK (fluticasone propionate and salmeterol)	• Available as an inhalation powder in three strengths • FDA-approved to treat asthma (all formulations/strengths) • May subject patients to lower fluticasone propionate exposure which may reduce oral candidiasis risk, and lower salmeterol exposure vs. ADVAIR DISKUS and ADVAIR HFA	• Administered twice daily • Not FDA-approved for treatment of COPD • Approved to treat asthma in patients aged ≥12 years; not in young children
BREO ELLIPTA (fluticasone furoate and vilanterol)	• Administered once daily • Indicated for maintenance treatment of airflow obstruction and for reducing COPD exacerbations (BREO ELLIPTA 100/25); also indicated to treat asthma (both strengths, adults only)	• Approved to treat asthma in patients aged ≥18 years; not in children
DULERA (mometasone furoate and formoterol fumarate dihydrate)	• Available in two strengths	• Administered twice daily • Not FDA-approved for treatment of COPD • Approved to treat asthma in patients aged ≥12 years
SYMBICORT (budesonide and formoterol fumarate dihydrate)	• Available in two strengths • FDA-approved to treat asthma (both strengths) and COPD (SYMBICORT 160/4.5) • FDA-approved to treat asthma in children aged 6 years and older	• Administered twice daily • Approved to treat asthma in patients aged ≥12 years • Not FDA-approved to reduce COPD exacerbations, only for maintenance treatment of airflow obstruction

REFERENCES

- Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared to fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40.
- Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.
- ADVAIR DISKUS prescribing information. GlaxoSmithKline. Research Triangle Park, NC. February 2017.
- ADVAIR HFA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. February 2017.
- Agusti A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2014;43(3):763-72.
- AIRDUO RESPICLICK prescribing information. Teva Respiratory, LLC. Frazer, PA. February 2017.
- Atienza T, Aquino T, Fernandez M, et al. Budesonide/formoterol maintenance and reliever therapy via Turbohaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma: Phase III study results. Respirology. 2013;18:354-63.
- Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. Am J Respir Crit Care Med. 2004;170(8):836-44.
- Bateman ED, Jacques L, Goldfrad C, et al. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006;117(3):563-70.
- Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69:312-19.
- Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med. 2001;95:136-46.
- Berger WE, Bleecker ER, O'Dowd L, et al. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. Allergy Asthma Proc. 2010;31:49-59.
- Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. J Asthma. 2015;52(10):1073-83.
- Bernstein DI, Hebert J, Cheema A, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. Allergy Asthma Clin Immunol. 2011;7(1):21.
- Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553-61.
- Bousquet J, Boulet Louis-Philippe, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs high-dose salmeterol/fluticasone. Respir Med. 2007:101:2437-46.
- BREO ELLIPTA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. May 2017.
- Busse WW, Shah SR, Somerville L, et al. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immuno. 2008;121:1407-14.
- Calhoun WJ, Nelson HS, Nathan RA, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta(2)-agonists alone. Am J Respir Crit Care Med. 2011;164(5):759-63.
- Calverley PMA ,Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89.
- Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 2003;361:449-56.
- Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease (COPD). Updated September 16, 2016. Available at: https://www.cdc.gov/copd/index.html. Accessed May 12, 2017.
- Chapman KR, Ringdal N, Backer V, et al. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J. 1999;6:45-51.
- Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta$_2$-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database of Systematic Reviews. 2014; Issue 1. Art. No.: CD003137. DOI: 10.1002/14651858.CD003137.pub5.
- CINQAIR prescribing information. Teva. Frazer, PA. March 2016.
- Corren J, Korenblat PE, Miller CJ, et al. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared to budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther. 2007;29(5):823-43.
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147(4):894-942.
- Dahl R, Chuchalin A, Gor D, et al. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Resp Med. 2006; 100:1152-62.
- Doherty DE, Tashkin DP, Kerwin E, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:57-71.
- Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Respir Med. 2013;1:210-23.
- Dransfield MT, Feldman G, Korenblat P, et al. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. Respir Med. 2014;108:1171-79.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed June 14, 2017.
- DULERA prescribing information. Merck Sharp & Dohme. Whitehouse Station, NJ. July 2016.
- Dwan K, Milan SJ, Bax L, et al. Vilanterol and fluticasone furoate for asthma. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD010758. DOI: 10.1002/14651858.CD010758.pub2.

- Eid NS, Noonan MJ, Chipps B, et al. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. Pediatrics. 2010;126:e565-e75.
- FDA AirDuo RespiClick Medical Review. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208799Orig1s000TOC.cfm. Accessed May 15, 2017.
- FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005;27(4):393-406.
- Gappa M, Zachgo W, von Berg A, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol. 2009;44:1132-42.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2017. Available from: ginasthma.org. Accessed May 12, 2017.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: 2017 report. Revised 2016. Available at: http://goldcopd.org/. Accessed December 5, 2016.
- Hanania N, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the discus inhaler for the treatment of COPD. Chest. 2003;124(3):834-43.
- Hanania NA, Crater GD, Morris AN, et al. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respir Med. 2012;106:91-101.
- Institute for Clinical Systems Improvement. Diagnosis and Management of Asthma. Published December 2016. Available at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_respiratory_guidelines/asthma/. Accessed June 15, 2017.
- Jenkins C, Kolarikova R, Kuna P, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared to budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006;11:276-86.
- Karner C, Cates CJ. Combination inhaled steroid and long-acting beta$_2$-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2011; Issue 3. Art. No.: CD008532. DOI: 0.1002/14651858.CD008532.pub2.
- Kerwin EM, Oppenheimer JJ, LaForce C, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. Ann Allergy Asthma Immunol. 2009;103:62-72.
- Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomized trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. Respir Med. 2013;107:560-69.
- Kew KM, Karner C, Mindus SM, et al. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD009019. DOI: 10.1002/14651858.CD009019.pub2.
- Kuna P, Creemers JPHM, Vondra V, et al. Once-daily dosing with budesonide/formoterol compared to twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. Respir Med. 2006;100(12):2151-9.
- Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007;61(5):725-36.
- Lalloo U, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared to increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest. 2003;123:1480-7.
- Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD004106. DOI: 10.1002/14651858.CD004106.pub4.
- Lazarinis N, Jorgensen L, Ekstrom T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax. 2014;69:130-6.
- Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. Respir Med. 2006;100:2-10.
- Marceau C, Lemiere C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol. 2006;118:574-81.
- Mansfield L, Yiu G, Sakov A, et al. A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. Allergy Asthma Proc. 2017 May 24.
- Maspero J, Guerra F, Cuevas F, et al. Efficacy and tolerability of salmeterol/fluticasone propionate vs montelukast in childhood asthma: a prospective, randomized, double-blind, double-dummy, parallel-group study. Clin Ther. 2008 Aug;30(8):1492-504.
- Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomized trial. Respir Med. 2013;107:550-9.
- Meltzer EO, Kuna P, Nolte H, et al., on behalf of the P04073 Study Investigators. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. Eur Respir J. 2012;39:279-89.
- Miller DS, Yiu G, Hellriegel ET, et al. Dose-ranging study of salmeterol using a novel fluticasone propionate/salmeterol multidose dry powder inhaler in patients with persistent asthma. Allergy Asthma Proc. 2016;37(4):291-301.
- Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. Int J Clin Pract. 2007;61(11):1874-83.
- Murphy K, Nelson H, Parasuraman B, et al. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. Curr Med Res Opin. 2008;24(3):879-94.
- Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus long-acting beta$_2$-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2012; Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub 2.
- Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD003794. DOI: 10.1002/14651858.CD003794.pub4.

- Nathan RA, Rooklin A, Schoaf L, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. Clin Ther. 2006;28:73-85.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed November 9, 2016.
- National Heart, Lung, and Blood Institute. What is Asthma? August 2014. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. Accessed November 9, 2016.
- Nelson HS, Chapman KR, Pyke SD, et al. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. J Allergy Clin Immunol. 2003(a);112:29-36.
- Nelson HS, Wolfe JD, Gross G, et al. Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. Ann Allergy Asthma Immunol. 2003(b);91:263-9.
- Noonan M, Rosenwasser LJ, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma. Drugs. 2006;66(17):2235-54.
- NUCALA prescribing information. GlaxoSmithKline. Research Triangle Park, NC. February 2017.
- O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43(3):773-82.
- Ohar JA, Crater GD, Emmett A, et al. Fluticasone propionate/salmeterol 250/50 µg versus salmeterol 50 µg after chronic obstructive pulmonary disease exacerbation. Respir Res. 2014;15:105. DOI:10.1186/s12931-014-0105-2.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 14, 2017.
- Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther. 2001;14(1):29-34.
- Partridge MR, Schuermann W, Beckman O, et al. Effect on lung function and morning activities of budesonide/formoterol vs salmeterol/fluticasone in patients with COPD. Ther Adv Respir Dis. 2009;3(4):147-57.
- Pearlman DS, Peden D, Condemi JJ, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. J Asthma. 2004;41:797-806.
- Perrin K, Williams M, Wijesinghe M, et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. J Allergy Clin Immunol. 2010;126:505-10.
- Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med. 2016;375:850-60.
- Pohl WR, Vetter N, Zwick H, et al. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. Respir Med. 2006;100(3):551-60.
- Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared to formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res. 2007;8:46.
- Quirce S, Barcina C, Plaza V, et al. A comparison of budesonide/formoterol maintenance and reliever therapy versus conventional best practice in asthma management in Spain. J Asthma. 2011;48:839-847.
- Rabe KF, Pizzichini E, Ställberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma. Chest. 2006;129(2):246-56.
- Raphael G, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers for persistent asthma [abstract no. P142]. Ann Allergy Asthma Immunol. 2016; 5(117):S63.
- Raphael G, Yiu G, Sakov A, et al. Patient-reported outcomes and quality of life improved with fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers versus placebo in patients with persistent asthma [abstract no. 31]. Abstract presented at AAAAI Annual Meeting; March 3-6, 2017; Atlanta, Georgia.
- Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. 2009;69(5):549-65.
- Riemersma RA, Postma D, van der Molen T. Budesonide/formoterol maintenance and reliver therapy in primary care asthma management: effects on bronchial hyperresponsiveness and asthma control. Prim Care Respir J. 2012;21(1):50-56.
- Ringdal N, Eliraz A, Pruzinec P, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respir Med. 2003;97:234-41.
- Rodrigo GJ, Plaza V, et al. Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2016;116:565-70.
- Rosenhall L, Heinig JH, Lindqvist A, et al. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. Int J Clin Pract. 2002;56(6):427-33.
- Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy vs a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004;20(9):1403-18.
- Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Ubaldo JM. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respir Med. 2012;106:257-68.
- Sher L, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma [abstract no. P139]. Ann Allergy Asthma Immunol. 2016; 5(117):S61-2.
- Sher L, Yiu G, Sakov A, et al. Treatment of asthmatic patients with fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo: patient-reported outcomes and quality of life [abstract no. 306]. Abstract presented at AAAAI Annual Meeting; March 3-6, 2017; Atlanta, Georgia.
- Soes-Petersen U, Kava T, Dahle R, et al. Budesonide/formoterol maintenance and reliever therapy versus conventional best standard treatment in asthma in an attempted 'real life' setting. Clin Respir J. 2011;5:173-82.
- SPIRIVA RESPIMAT prescribing information. Boehringer Ingelheim. Ridgefield, CT. February 2017.

- Stempel DA, Raphiou IH, Kral KM, et al. Serious adverse events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med. 2016(a);374:1822-30.
- Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. N Engl J Med. 2016(b);375:840-9.
- SYMBICORT prescribing information. AstraZeneca. Wilmington, DE. January 2017.
- Tashkin DP, Doherty DE, Kerwin E, et al. Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate to very severe COPD: results from a 52-week Phase III trial. Int J Chron Obstruct Pulmon Dis. 2012;7:43-55.
- Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. Drugs. 2008;68(14):1975-2000.
- Tal A, Simon G, Vermeulen, JH, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol. 2002;34:342-50.
- Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. Am J Respir Crit Care Med. 2010;182:1221-7.
- Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016(a);387:1817-26.
- Vestbo J, Leather D, Bakerly ND, et al. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. N Engl J Med. 2016(b);375:1253-60.
- Vestbo J, Pauwels R, Anderson J, et al. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax. 2005;60:301-4.
- Vogelmeier C, Naya I, Ekelund J. Budesonide/formoterol maintenance and reliever therapy in Asian patients (aged >16 years) with asthma. Clin Drug Investig. 2012;32(7):439-49.
- Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med. 2016;374(23):2222-34.
- Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177:19-26.
- Weinstein SF, Corren J, Murphy K, et al. Twelve–week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. Allergy Asthma Proc. 2010;31:280-9.
- Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:741-50.
- Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144(4):1222-9.
- Zangrilli J, Mansfield LE, Uryniak T, et al. Efficacy of budesonide/formoterol pressurized metered-dose inhaler vs budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial. Ann Allergy Asthma Immunol. 2011;107(3):258-65.e2.
- Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:1015-26.

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Therapeutic Class Overview
Cardiovascular, Angiotensin II Receptor Blockers (ARBs) – Combination Products

SCOPE OF REVIEW

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- An estimated 85.7 million Americans or 34% of US adults aged ≥20 years have high blood pressure (BP). Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Benjamin et al, 2017).
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI) improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Benjamin et al, 2017).
- Left ventricular (LV) hypertrophy is the enlargement of the ventricle muscle tissue. Often LV hypertrophy develops due to high blood pressure, which requires the ventricle to increase the workload, resulting in thickening of the chamber walls. LV hypertrophy often progresses to heart failure (HF) (Lorell et al, 2000).
- Lowering of blood pressure has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI). Improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Go et al, 2014).
- Numerous classes of antihypertensives are available to reduce blood pressure. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta blockers, and calcium channel blockers (CCBs). Selection of an antihypertensive for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, diabetes (DM), chronic kidney disease (CKD), prevention of recurrent stroke, post-MI, and patients with high risk for coronary heart disease (CHD). Some patients require two or more antihypertensives from different pharmacological classes to achieve blood pressure control (Go et al, 2014; James et al, 2013; Weber et al, 2014). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥ 50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over the period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of MI, acute coronary syndrome (ACS), stroke, HF, or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- This review will focus on the combination of ARB with a beta blocker, CCB, diuretic, or both a diuretic and a CCB for the management of hypertension. The ARB combination products are Food and Drug Administration (FDA) approved for the treatment of hypertension. Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and LV hypertrophy. The products available in this class include various combinations of an ARB with a beta blocker (nebivolol), CCB (amlodipine), a diuretic (HCTZ or chlorthalidone), or both HCTZ and amlodipine. TEVETEN HCT is no longer available.
- Medispan class: Antihypertensive Combinations. Three subcategories include ARB/CCB combinations, beta blocker/ARB combination, ARB/thiazide and thiazide-like combinations, and ARB/CCB/thiazide combinations.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ARB/Diuretic Combinations			
ATACAND HCT® (candesartan/hydrochlorothiazide)	various	09/05/2000	✔
AVALIDE® (irbesartan/hydrochlorothiazide)*	various	09/30/1997	✔
BENICAR HCT® (olmesartan/hydrochlorothiazide)	various	06/05/2003	✔
DIOVAN HCT® (valsartan/hydrochlorothiazide)†	various	03/06/1998	✔
EDARBYCLOR® (azilsartan/chlorthalidone)	Takeda Pharmaceutical	12/20/2011	-
HYZAAR® (losartan/hydrochlorothiazide)	various	04/28/1995	✔
MICARDIS HCT® (telmisartan/hydrochlorothiazide)	various	11/17/2000	✔
ARB/Beta Blocker Combination			
BYVALSON® (valsartan/nebivolol)	Allergan/Forest Laboratories	06/03/2016	-
ARB/CCB Combinations			
AZOR® (olmesartan/amlodipine)	various	09/26/2007	✔
EXFORGE® (valsartan/amlodipine)	various	06/20/2007	✔
TWYNSTA® (telmisartan/amlodipine)	various	10/16/2009	✔
ARB/CCB/Diuretic Combinations			
EXFORGE® HCT (valsartan/amlodipine/ hydrochlorothiazide)	various	04/30/2009	✔
TRIBENZOR® (olmesartan/amlodipine/ hydrochlorothiazide)	various	07/23/2010	✔

*As of November 2016, Mylan has made a business decision to discontinue the manufacturing of this generic drug. Other generic products are available for this drug.
†As of February 2016, Sandoz discontinued the manufacturing of film-coated tables for this generic drug. Other generic products are available for this drug.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Hypertension	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
ARB/Diuretic Combinations		
ATACAND HCT (candesartan/hydrochlorothiazide)	✔ *	-
AVALIDE (irbesartan/hydrochlorothiazide)	✔ †	-
BENICAR HCT (olmesartan/hydrochlorothiazide)	✔ *	-
DIOVAN HCT (valsartan/hydrochlorothiazide)	✔ †	-
EDARBYCLOR (azilsartan/chlorthalidone)	✔ †	-
HYZAAR (losartan/hydrochlorothiazide)	✔ ‡	✔ §
MICARDIS HCT (telmisartan/hydrochlorothiazide)	✔ *	-

ARB/Beta Blocker Combination		
BYVALSON (valsartan/nebivolol)	✔ †	-
ARB/CCB Combinations		
AZOR (olmesartan/amlodipine)	✔ †	-
EXFORGE (valsartan/amlodipine)	✔ †	-
TWYNSTA (telmisartan/amlodipine)	✔ †	-
ARB/CCB/Diuretic Combinations		
EXFORGE HCT (valsartan/amlodipine/ hydrochlorothiazide)	✔ *	-
TRIBENZOR (olmesartan/amlodipine/ hydrochlorothiazide)	✔ *	-

*This fixed-dose combination is not indicated for initial therapy.
†Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

(Prescribing information: ATACAND HCT, 2016; AVALIDE, 2016; AZOR, 2017; BENICAR HCT, 2016; BYVALSON, 2016; DIOVAN HCT, 2015; EDARBYCLOR, 2016; EXFORGE, 2015; EXFORGE HCT, 2015; HYZAAR, 2015; MICARDIS HCT, 2016; TRIBENZOR, 2017; TWYNSTA, 2016)

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials assessing the combination ARBs in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus a diuretic (either HCTZ or chlorthalidone) or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or diuretics (Sachse et al, 2002; Neutel et al, 2006; Neutel et al, 2008; Neutel et al, 2012; Salerno et al, 2004; Chrysant et al, 2004; Chrysant et al, 2008; Littlejohn et al, 2009; Sharma et al, 2007[a]; Sharma et al, 2012; Destro et al, 2008; Philipp et al, 2007; Flack et al, 2009; Waeber et al, 2001; Zhu et al, 2012; Derosa et al, 2013). A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy (Conlin et al, 2000).
- Trials assessing triple therapy regimens with an ARB, amlodipine, and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy (Destro et al, 2010; Calhoun et al, 2009[a]; Calhoun et al, 2009[b]; Ohma et al, 2000; Wright et al, 2011).
- The safety and efficacy of nebivolol/valsartan 5/80 mg was based on a double-blind, placebo-controlled, parallel-group, dose-escalating, Phase 3, randomized controlled trial in 4,159 patients with Stage 1 or 2 hypertension. Patients were randomized to 1 of 4 treatment arms (with a total of 7 dose groups plus placebo): (1) nebivolol/valsartan (5/80 mg, 5/160 mg, or 10/160 mg); (2) nebivolol monotherapy (5 mg or 20 mg); (3) valsartan monotherapy (160 mg or 320 mg); or (4) placebo. All treatment was administered in fixed doses once per day for 4 weeks; doses were then doubled for weeks 5 to 8 of treatment. Compared to placebo, nebivolol/valsartan 5/80 mg significantly lowered systolic blood pressure (SBP) by 8.3 mmHg and diastolic blood pressure (DBP) by 7.2 mmHg, monotherapy with nebivolol 5 mg lowered SBP by 4.7 mmHg and DBP by 4.4 mmHg, and monotherapy with valsartan 80 mg lowered SBP by 5.4 mmHg and DBP by 3.9 mmHg after 4 weeks of treatment. Higher doses of the combination did not lead to further clinically meaningful reductions in BP. No adverse events were observed more frequently with nebivolol/valsartan compared to placebo. As anticipated with beta blocker and ARB therapy, serious adverse reactions such as hypotension or hyperkalemia may occur (Giles et al, 2014).

- Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class (Ambrosioni et al, 2010; Bobrie et al, 2005; Cushman et al, 2012; Derosa et al, 2013; Fogari et al, 2006; Lacourcière et al, 2003; Ohma et al, 2000; Sharma et al, 2007[b]; Toh et al, 2016; White et al, 2008; Wright et al, 2011).

SAFETY SUMMARY

- ARB combinations are contraindicated in patients with hypersensitivity to any of the components. In general, ARB combinations with HCTZ are contraindicated in patients with anuria. ARB-containing products should not be administered in combination with aliskiren in patients with diabetes (TEKTURNA®).
- All ARB-containing products have a boxed warning that states that use during pregnancy should be avoided. When pregnancy is detected, discontinue the ARB combination as soon as possible. Drugs that act directly on the renin-angiotensin system (RAS) can cause injury and death to the developing fetus.
- Dual blockade of the RAS with ARBs, ACE-Is, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors.
- ARB-containing products may cause hypotension, electrolyte abnormalities, and renal impairment.
- Nebivolol/valsartan is also contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and severe hepatic impairment.
- Common adverse events of ARB-containing products include hypotension, dizziness, headache, rash, pain, and cough.
- Edema is more commonly associated with amlodipine.
- Drug interactions with ARB-containing products include lithium (increase in lithium levels) and non-steroidal anti-inflammatory drugs (NSAIDs) (reduced ARB and diuretic effects and increased risk of renal injury or impairment). See prescribing information for full descriptions.
- Data from one controlled trial (ROADMAP) and an epidemiologic study (ORIENT) have suggested that high-dose BENICAR (olmesartan 40 mg daily) may increase cardiovascular (CV) risk in diabetic patients. The FDA safety review found no clear evidence of increased cardiovascular risks associated with olmesartan and determined the benefits outweighed the risks in patients with diabetes (BENICAR HCT prescribing information, 2016; Haller et al, 2011; Imai et al, 2011; FDA Drug Safety Communication: Safety Announcement, 2010; Safety Announcement, 2011; Safety Announcement, 2014).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ARB/Diuretic Combinations				
ATACAND HCT (candesartan/ HCTZ)	Tablet: 16/12.5 mg 32/12.5 mg 32/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	Patients not controlled or experiencing hypokalemia on HCTZ 25 mg can expect an incremental effect from 16/12.5 mg; patients not controlled on candesartan 32 mg can expect incremental blood pressure effects from	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			32/12.5 mg and 32/25 mg.	
AVALIDE (irbesartan/ HCTZ)	Tablet: 150/12.5 mg 300/12.5 mg	Hypertension†: Initial: 150/12.5 mg daily; may increase dose after 1 to 2 weeks to a maximum of 300/25 mg daily.	For patients not controlled on monotherapy with irbesartan or HCTZ, the recommended doses, in order of increasing mean effect, are 150/12.5, 300/12.5 and 300/25 mg.	May administer with or without food.
BENICAR HCT (olmesartan/ HCTZ)	Tablet: 20/12.5 mg 40/12.5 mg 40/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	For patients not controlled on olmesartan, HCTZ may be added starting with a dose of 12.5 mg and later titrated to 25 mg daily; if patient is taking HCTZ, olmesartan may be added starting with a dose of 20 mg daily and titrated to 40 mg. Administer only one tablet daily.	-
DIOVAN HCT (valsartan/ HCTZ)	Tablet: 80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg	Hypertension†: Initial: 160/25 mg daily; maximum, 320/25 mg daily.	Patients not controlled on valsartan or HCTZ monotherapy may switch to combination therapy.	-
EDARBYCLOR (azilsartan/ chlorthalidone)	Tablet: 40/12.5 mg 40/25 mg	Hypertension†: Initial: 40/12.5 mg daily. May increase dose to 40/25 mg after 2 to 4 weeks as needed to achieve blood pressure goals. Doses above 40/25 mg are probably not useful.	Patients not controlled with azilsartan may have an additional blood pressure reduction when switched to 40/12.5 mg. Patients not controlled with chlorthalidone 25 mg have further BP reduction when switched to 40/12.5 mg.	May administer with or without food.
HYZAAR (losartan/ HCTZ)	Tablet: 50/12.5 mg 100/12.5 mg 100/25 mg	Hypertension‡: Initial: 50/12.5 mg daily; maintenance, if blood pressure remains uncontrolled, the dose may be increased to 2	LV Hypertrophy with Hypertension§: If additional BP reduction is needed, losartan 100 mg and HCTZ 12.5 mg or	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		tablets of 50/12.5 mg daily or 1 tablet of 100/25 mg daily; maximum, 100/25 mg/day. LV hypertrophy in hypertensive patients§: Initial: losartan 50 mg daily; if blood pressure is not adequately controlled, increase to 50/12.5 mg daily; maximum, 100/25 mg/day.	100/12.5 mg may be substituted, followed by losartan 100 mg and HCTZ 25 mg or 100/25 mg.	
MICARDIS HCT (telmisartan/ HCTZ)	Tablet: 40/12.5 mg 80/12.5 mg 80/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components.	Patients not controlled on telmisartan 80 mg monotherapy may be switched to 80/12.5 mg daily and titrated up to 160/25 mg if necessary; patients not controlled on HCTZ 25 mg may be switched to 80/12.5 or 80/25 mg daily.	May administer with or without food.
ARB/Beta Blocker Combination				
BYVALSON (valsartan/ nebivolol)	Tablet: 80/5 mg	Hypertension†: Initial or in patient adequately controlled on valsartan ≤80 mg or nebivolol ≤10 mg: 80/5 mg once daily; maximum, 80/5 mg daily; combination may be substituted for the titrated individual components.	Maximum antihypertensive effects are attained within 2 to 4 weeks.	May administer with or without food.
ARB/CCB Combinations				
AZOR (olmesartan/ amlodipine)	Tablet: 20/5 mg 40/5 mg 20/10 mg 40/10 mg	Hypertension†: Initial: 20/5 mg daily; maximum, 40/10 mg daily; combination may be substituted for the titrated individual components.	Dosages may be increased after 2 weeks. Initial therapy with AZOR is not recommended in patients ≥75 years old or with hepatic impairment.	May administer with or without food.
EXFORGE (valsartan/ amlodipine)	Tablet: 160/5 mg 160/10 mg 320/5 mg	Hypertension†: Initial: 160/5 mg daily; maximum, 320/10 mg daily; combination may	The dosage can be increased after 3 to 4 weeks of therapy to a maximum of one	May administer with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	320/10 mg	be substituted for the titrated individual components.	320/10 mg tablet once daily as needed to control blood pressure.	
TWYNSTA (telmisartan/ amlodipine)	Tablet: 40/5 mg 40/10 mg 80/5 mg 80/10 mg	Hypertension†: Initial: 40/5 mg daily, patients requiring larger blood pressure reductions may be started at 80/5 mg daily; combination may be substituted for the titrated individual components; maximum, 80/10 mg daily.	The dosage can be increased after at least 2 weeks to a maximum of 80/10 mg once daily.	May administer with or without food.
ARB/CCB/Diuretic Combinations				
EXFORGE HCT (valsartan/ amlodipine/ HCTZ)	Tablet: 160/5/12.5 mg 160/5/25 mg 160/10/12.5 mg 160/10/25 mg 320/10/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 320/10/25 mg daily.	The dosage may be increased after 2 weeks of therapy. The full BP lowering effect was achieved 2 weeks after being on the maximal dose of EXFORGE HCT.	EXFORGE HCT may be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, ARBs, and diuretics. May administer with or without food.
TRIBENZOR (olmesartan/ amlodipine/ HCTZ)	Tablet: 20/5/12.5 mg 40/5/12.5 mg 40/5/25 mg 40/10/12.5 mg 40/10/25 mg	Hypertension*: Initial: initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 40/10/25 mg.	The dosage can be increased after at least 2 weeks to a maximum of 40/10/25 mg once daily.	May be used for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, ARBs, and diuretics. May administer with or without food.

*This fixed-dose combination is not indicated for initial therapy.
†Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ARB/Diuretic Combinations					
ATACAND HCT (candesartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	Safety and effectiveness in patients with severe renal impairment (CrCL ≤30 mL/min) have not been established.	Consider lower starting dose of 8 mg in patients with moderate hepatic impairment; however, this dose is not available with the HCTZ combination.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
AVALIDE (irbesartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. AVALIDE is not recommended.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
BENICAR HCT (olmesartan/ HCTZ)	Dosing should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased organ function and other diseases or drug therapy.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred over HCTZ. BENICAR HCT is not recommended.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
DIOVAN HCT (valsartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	Safety and efficacy in patients with severe renal impairment (CrCL ≤30 mL/min) have not been established.	No dosage adjustment required. No data in severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
EDARBYCLOR (azilsartan/ chlorthalidone)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	No dosage adjustment required. Safety and effectiveness in patients with severe renal impairment (estimated GFR	No dosage adjustment required. Not studied in severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk;

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			<30 mL/min/1.73 m^2) have not been established.		discontinue drug or nursing.
HYZAAR (losartan/HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. HYZAAR is not recommended.	Not recommended in hepatic impairment as the lower starting dose of losartan is not available in HYZAAR.	Pregnancy Category: C (first trimester) Pregnancy Category: D (second and third trimester) Unknown whether excreted in breast milk; discontinue drug or nursing.
MICARDIS HCT (telmisartan/ HCTZ)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	In patients with CrCL ≤30 mL/min, loop diuretics are preferred to thiazides. MICARDIS HCT is not recommended.	Not recommended in severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg dose.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
ARB/Beta Blocker Combination					
BYVALSON (valsartan/ nebivolol)	No dosage adjustment required in the elderly population.	Safety and efficacy in children have not been established.	No dosage adjustment required for mild to moderate renal impairment. Not recommended in severe renal impairment.	Not recommended in moderate to severe hepatic impairment.	Can cause fetal harm. Discontinue if pregnancy is detected. Beta blockers have potential to affect nursing infants; discontinue drug or nursing.
ARB/CCB Combinations					
AZOR (olmesartan/ amlodipine)	No dosage adjustment required in the elderly population. Initial therapy is not recom-mended in	Safety and efficacy in children have not been established.	No dosage adjustment required for mild to moderate renal impairment (CrCL<40 mL/min).	Initiate amlodipine at 2.5 mg in patients with severe hepatic impairment, which is not available with AZOR. Initial therapy is not recommended in	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	patients ≥75 years of age.			hepatically impaired patients.	
EXFORGE (valsartan/ amlodipine)	Consider lower doses in the elderly population.	Safety and efficacy in children have not been established.	Safety and effectiveness for CrCL <30 mL/min has not been established.	Lower initial doses of amlodipine may be required in patients with hepatic impairment. Not recommended for initial therapy.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TWYNSTA (telmisartan/ amlodipine)	No dosage adjustment required in the elderly population. Initial therapy is not recom-mended in patients ≥75 years of age.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate amlodipine at 2.5 mg in patients with severe hepatic impairment. Initial therapy is not recommended in hepatically impaired patients. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
ARB/CCB/Diuretic Combinations					
EXFORGE HCT (valsartan/ amlodipine/ HCTZ)	Consider lower doses in the elderly population.	Safety and efficacy in children have not been established.	Safety and efficacy in patients with renal impairment (CrCL <30 mL/min) have not been established.	Lower starting doses of amlodipine may be required in patients with hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TRIBENZOR (olmesartan/ amlodipine/ HCTZ)	No dosage adjustment required in the elderly population. Patients ≥75 years of age should start amlodipine at 2.5 mg, which is not available with TRIBENZOR.	Safety and efficacy in children have not been established.	No dosage adjustment required. Avoid use in patients with CrCL<30 mL/min.	Initiate amlodipine at 2.5 mg in patients with severe hepatic impairment, which is not available with TRIBENZOR. Initial therapy is not recommended in hepatically impaired patients.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Abbrv: CrCL=creatinine clearance, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, LV=left ventricular

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.

CONCLUSION

- The ARB combination products are Food and Drug Administration (FDA)-approved for the treatment of hypertension. HYZAAR is also indicated for stroke prophylaxis in hypertensive patients with left ventricular hypertrophy.
- The products available in this class include various combinations of an ARB with a beta blocker (nebivolol), calcium channel blocker (amlodipine), chlorthalidone, a thiazide diuretic (HCTZ) or both HCTZ and amlodipine, and there are several generics available in this class.
- Losartan/HCTZ is the only combination agent in the class which carries an additional indication for reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. The efficacy of losartan in preventing stroke in this population was demonstrated in the Losartan Intervention for Endpoint trial and its corresponding substudies. Losartan was compared to therapy with atenolol (HCTZ could be added to primary regimens if needed for blood pressure control). Results demonstrate a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as compared to atenolol-based regimens (Dahlöf et al, 2002).
- Clinical trials assessing the ARB combination products in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ, nebivolol, or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, nebivolol, amlodipine or HCTZ. A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy (Conlin et al, 2000). Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy (Destro et al, 2010; Calhoun et al, 2009[b]; Ohma et al, 2000). Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class (Ambrosioni et al, 2010; Bobrie et al, 2005; Fogari et al, 2006; Giles et al, 2014; Lacourcière et al, 2003; Ohma et al, 2000; Sharma et al, 2007[b]; White et al, 2008).
- Evidence-based guidelines recognize the important role ARBs, beta blockers, CCBs and diuretics play in the treatment of hypertension and other cardiovascular and renal diseases. There is no consensus on blood pressure goals for certain populations, such as older patients, patients with diabetes, and/or CKD. Combination therapy is recommended once the initial drug is titrated to maximum and the goal blood pressure is not reached (Go et al, 2014; James et al, 2013; Mancia et al, 2013; Weber et al, 2014). The guidelines also differ on first-line treatment options in various groups. Treatment is generally recommended based on agents in the class. The current treatment guidelines do not make recommendations based on combination therapy:
  - In black hypertensive patients, thiazide-type diuretics or CCBs are recommended as first line therapy and in non-black patients ACE-Is or ARBs, CCBs, and thiazides are options for initiating treatment, although some guidelines recommend ACE-Is or ARBs in non-black patients only (Go et al, 2014; James et al, 2013; Mancia et al, 2013; Piepoli et al, 2016; Rosendorff et al, 2015; Weber et al, 2014).
  - ACE-Is or ARBs are recommended as a first-line option in patients with chronic kidney disease (CKD) with or without proteinuria, due to its renal protective attributes. Combination therapy may be most useful in patients without electrolyte abnormalities and dihydropyridine CCBs may not be appropriate in patients with increased urinary albumin excretion (Go et al, 2014; Mancia et al, 2013; James et al, 2013; KDIGO, 2012; Weber et al, 2014).
  - ACE-Is or ARBs are also recommended as a first-line therapy option in heart failure, for patients post-myocardial infarction, and in cases of left ventricular dysfunction, unless otherwise contraindicated (Go et al, 2014; Hamm et al, 2011; O'Gara et al, 2013; Montalescot et al, 2013; Ponikowski et al, 2016; Roffi et al, 2016; Steg et al, 2012; Stout et al, 2016; Weber et al, 2014; Windecker et al, 2014; Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017).
  - In general, reputable guidelines recommend the combination of a beta blocker and ARB as an option in patients with hypertension and coronary artery disease post-MI regardless of BP or HF (Go et al, 2014; James et al, 2013; Weber et al, 2014).

REFERENCES

- Ambrosioni E, Bombelli M, Cerasola G, et al. Ambulatory monitoring of systolic hypertension in the elderly: eprosartan/hydrochlorothiazide compared to losartan/hydrochlorothiazide (INSIST trial). Adv Ther. 2010;27(6):365-80.
- ATACAND HCT prescribing information. AstraZeneca; Wilmington, DE; July 2016.
- AVALIDE prescribing information. Sanofi-Aventis U.S. LLC; Bridgewater, NJ; February 2016.
- AZOR prescribing information. Daiichi Sankyo Inc.; Parsippany, NJ; January 2017.
- BENICAR HCT prescribing information. Daiichi Sankyo Inc. Parsippany, NJ; February 2016.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Bobrie G, Delonca J, Moulin C, et al. A home blood pressure monitoring study comparing the antihypertensive efficacy of two angiotensin II receptor antagonist fixed combinations. Am J Hypertens. 2005;18:1482-8.
- BYVALSON prescribing information. Allergan USA, Inc.; Irvine, CA; June 2016.
- Calhoun D, Crikelair N, Yen J, et al. Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: secondary analyses evaluating efficacy and safety. Adv Ther. 2009[a];26(11):1012-23.
- Calhoun D, Lacourcière Y, Chiang Y, et al. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide - a randomized clinical trial. Hypertension. 2009[b];54:32-9.
- Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther. 2008;30(4):587-604.
- Chrysant SG, Weber MA, Wang AC, et al. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. Am J Hypertens. 2004;17(3):252-9.
- Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? Am J Hypertens. 2000;13(4 Pt 1):418-26.
- Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in Stage 2 Systolic Hypertension. Hypertension. 2012 Aug;60(2):310-8. doi: 10.1161/HYPERTENSIONAHA.111.188284.
- Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet. 2002;359(9311):995-1003.
- Derosa G, Cicero AF, Carbone A, et al. Results from a 12 months, randomized, clinical trial comparing an olmesartan/amlodipine single pill combination to olmesartan and amlodipine monotherapies on blood pressure and inflammation. Eur J Pharm Sci. 2014 Jan 23;51:26-33.
- Destro M, Crikelair N, Yen J, et al. Triple combination therapy with amlodipine, valsartan and hydrochlorothiazide vs dual combination therapy with amlodipine and hydrochlorothiazide for stage 2 hypertensive patients. Vasc Health Risk Manag. 2010;6:821-7.
- Destro M, Luckow A, Samson M, et al. Efficacy and safety of amlodipine/valsartan compared to amlodipine monotherapy in patients with stage 2 hypertension: a randomized, double-blind, multicenter study: the EX-EFFeCTS study (abstract). J Am Soc Hypertens. 2008;2(3):294-302.
- DIOVAN HCT prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ; July 2015.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 26, 2017.
- EDARBYCLOR prescribing information. Takeda Pharmaceuticals America, Inc.; Deerfield, IL; March 2016.
- EXFORGE HCT prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ; July 2015.
- EXFORGE prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ; August 2015.
- Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared to amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study (abstract). Journal of Human Hypertension. 2009;23(7):479-89.
- Fogari R, Zoppi A, Mugellini A, et al. Hydrochlorothiazide added to valsartan is more effective than when added to olmesartan in reducing blood pressure in moderately hypertensive patients inadequately controlled by monotherapy. Adv Ther. 2006;23(5):680-95.
- Food and Drug Administration (FDA) Drug Safety Communication. FDA Drug Safety Communication: Ongoing safety review of Benicar (olmesartan) and cardiovascular events. [safety announcement]. June 11, 2010. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm215222.htm. Accessed May 26, 2017.
- FDA Drug Safety Communication. FDA Drug Safety Communication: Safety review update of Benicar (olmesartan) and cardiovascular events. [safety announcement]. April 14, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251268.htm. Accessed May 26, 2017.
- FDA Drug Safety Communication. FDA Drug Safety Communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required. [safety announcement]. June 24, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm402323.htm. Accessed May 26, 2017.
- Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomized, multicenter study. Lancet. 2014;383:1889-98.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). Hypertension. 2014 Apr;63(4):878-85.
- Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in Type 2 Diabetes. N Engl J Med 2011;364:907-17.
- HYZAAR prescribing information. Merck & Co. Inc.; Whitehouse Station, NJ; December 2015.
- Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicenter, randomized, placebo-controlled study. Diabetologia. 2011 Dec;54(12):2978-86.
- James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414.

- Lacourcière Y, Gil-Extremera B, Mueller O, et al. Efficacy and tolerability of fixed-dose combinations of telmisartan plus HCTZ compared to losartan plus HCTZ in patients with essential hypertension. Int J Clin Pract. 2003;57(4):273-9.
- Littlejohn T, Majul C, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich). 2009;11(4):207-13.
- Lorell BH, et al. Left ventricular hypertrophy: Pathogenesis, detection, and prognosis. Circulation. 2000;102:470
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
- MICARDIS HCT prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT; January 2016.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2949-3003.
- Neutel JM, Franklin SS, Lapuerta P, et al. A comparison of the efficacy and safety of irbesartan/HCTZ combination therapy with irbesartan and HCTZ monotherapy in the treatment of moderate hypertension. J Hum Hypertens. 2008;22(4):266-74.
- Neutel JM, Franklin SS, Oparil S, et al. Efficacy and safety of irbesartan/HCTZ combination therapy as initial treatment for rapid control of severe hypertension. J Clin Hypertens (Greenwich). 2006;8(12):850-7.
- Neutel JM, Mancia G, Black HR, et al for the TEAMSTA Severe HTN Study Investigators. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012 Apr;14(4):206-15.
- Ohma KP, Milon H, Valnes K. Efficacy and tolerability of a combination tablet of candesartan cilexetil and hydrochlorothiazide in insufficiently controlled primary hypertension--comparison with a combination of losartan and hydrochlorothiazide. Blood Press. 2000;9(4):214-20.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 31, 2017.
- Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007;29(4):563-80.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;27(29):2315-2381.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 May 20. pii: ehw128. doi: http://dx.doi.org/10.1093/eurheartj/ehw128
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267-315.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of Hypertension in Patients with Coronary Artery Disease: A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). J Am Coll Cardiol. May 2015;65(18):1998-2038. doi:10.1016/j.jacc.2015.02.038.
- Sachse A, Verboom C, Jager B. Efficacy of eprosartan in combination with HCTZ in patients with essential hypertension. J Hum Hypertens. 2002;16:169-76.
- Salerno CM, Demopoulos L, Mukherjee R, et al. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. J Clin Hypertens (Greenwich). 2004;6(11):614-20.
- Sharma A, Bagchi A, Kinagi S, et al. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine versus amlodipine monotherapy in Indian adults with stage II hypertension. Clin Ther. 2007[a];29(12);2667-76.
- Sharma AM, Bakris G, Neutel JM, et al. Single-pill combination of telmisartan/amlodipine versus amlodipine monotherapy in diabetic hypertensive patients: an 8-week randomized, parallel-group, double-blind trial. Clin Ther. 2012;34(3):537-51.
- Sharma AM, Davidson J, Koval S, et al. Telmisartan/hydrochlorothiazide versus valsartan/hydrochlorothiazide in obese hypertensive patients with type 2 diabetes: the SMOOTH study. Cardiovasc Diabetol. 2007[b];6:28.
- SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26; 373(22):2103-16.
- Stout KK, Broberg CS, Book WM, et al. American Heart Association (AHA) Scientific Statement: Chronic Heart Failure in Congenital Heart Disease. Circulation. 2016;133:770-801.
- Toh N, Ishii K, Kihara H, et al; Effect of ARB/Diuretics on Diastolic Function in Patients with Hypertension 2 (EDEN2) trial investigators. Effect of diuretic or calcium-channel blocker plus angiotensin-receptor blocker on diastolic function in hypertensive patients. Circ J. 2016;80(2):425-434.
- TRIBENZOR prescribing information. Daiichi Sankyo Inc.; Parsippany, NJ; January 2017.
- TWYNSTA prescribing information. Boehringer Ingelheim Pharmaceuticals Inc.; January 2016.
- Waeber B, Aschwanden R, Sadecky L, et al. Combination of hydrochlorothiazide or benazepril with valsartan in hypertensive patients unresponsive to valsartan alone. J Hypertens. 2001;19(11):2097-104.
- Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014 Jan;32(1):3-15.
- White WB, Murwin D, Chrysant SG, et al. Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: a large, confirmatory trial. Blood Press Monit. 2008;13(1):21-7.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed

with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541-619.
- Wright RF, Duprez D, Purkayastha D, et al. Combination angiotensin-receptor blocker (ARB)/calcium channel blocker with HCTZ vs the maximal recommended dose of an ARB with HCTZ in patients with stage 2 hypertension: the Exforge as compared to losartan treatment in stage 2 systolic hypertension (EXALT) study. J Clin Hypertens (Greenwich). 2011 Aug;13(8):588-97.
- Yancy CW, Jessup M, Bozkurk B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013. DOI: 10.1016/j.jacc.2013.05.020.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Apr 25. doi: 10.1016/j.cardfail.2017.04.014.
- Zhu DL, Bays H, Gao P, et al. Efficacy and tolerability of initial therapy with single-pill combination telmisartan/hydrochlorothiazide 80/25 mg in patients with grade 2 or 3 hypertension: a multinational, randomized, double-blind, active-controlled trial. Clin Ther. 2012 Jul;34(7):1613-24. doi: 10.1016/j.clinthera.2012.05.007.

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Therapeutic Class Overview
Angiotensin II Receptor Blockers (ARBs) Single Entity Agents

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- An estimated 85.7 million Americans or 34% of US adults aged ≥20 years have high blood pressure (BP). Hypertension is an independent risk factor for cardiovascular disease and increases the mortality risks of cardiovascular disease and other diseases (Benjamin et al, 2017).
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal cardiovascular events including stroke and myocardial infarctions (MI) improving cardiovascular health and reducing cardiovascular risk also includes lipid control, diabetes management, smoking cessation, exercise, weight management, and limited sodium intake (Benjamin et al, 2017).
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta (β)-blockers, and calcium channel blockers (CCBs). Selection of an antihypertensive for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as heart failure (HF), diabetes (DM), chronic kidney disease (CKD), prevention of recurrent stroke, post-MI, and patients with high risk for coronary heart disease (CHD). Some patients require two or more antihypertensives from different pharmacological classes to achieve BP control (Go et al, 2013; Weber et al, 2014; James et al, 2013). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over the period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of MI, acute coronary syndrome (ACS), stroke, HF, or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- This review will focus on the ARBs which are Food and Drug Administration (FDA) approved to treat hypertension, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine (SCr) and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular (LV) hypertrophy for cardiovascular risk reduction in patients unable to take ACE-Is, and to reduce the risk of cardiovascular mortality in clinically stable patients with LV failure or LV dysfunction following MI.
- Medispan Therapeutic Class: Angiotensin II Receptor Antagonists

Table 1. Medications Included Within ARB Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ATACAND® (candesartan)	various	06/4/1998	✔
AVAPRO® (irbesartan)	various	09/30/1997	✔
BENICAR® (olmesartan)	various	04/25/2002	✔
COZAAR® (losartan)	various	04/14/1995	✔
DIOVAN® (valsartan)	various	07/18/2001 (tablet)	✔
EDARBI® (azilsartan)	Takeda	02/25/2011	-
MICARDIS® (telmisartan)	various	11/10/1998	✔
TEVETEN®* (eprosartan)	various	12/22/1997	✔

*Brand name eprosartan (TEVETEN) is no longer available.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ATACAND (candesartan)	AVAPRO (irbesartan)	BENICAR (olmesartan)	COZAAR (losartan)	DIOVAN (valsartan)	EDARBI (azilsartan)	MICARDIS (telmisartan)	TEVETEN# (eprosartan)
Hypertension in adults – may be used alone or in combination.	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children ages 1 to < 17 years – may be used alone or in combination. Lowering BP reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and MI.	✔							
Hypertension in children ages 6 to 16 years – may be used alone or in combination.			✔	✔	✔			
Treatment of diabetic nephropathy with an elevated SCr and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, AVAPRO and COZAAR reduce the rate of progression of nephropathy as measured by the occurrence of doubling of SCr or end-stage renal disease (need for dialysis or renal transplantation).		✔		✔				
Heart failure (NYHA Class II to IV) – reduces cardiovascular death and heart failure hospitalization.	✔							
Heart failure (NYHA Class II to IV) in adults - to reduce the risk of hospitalizations for heart failure.					✔			
Reduction in the risk of stroke in patients with hypertension and LV hypertrophy.				✔				
Post MI: In clinically stable patients with LV failure or LV dysfunction following MI, DIOVAN is indicated to reduce cardiovascular mortality.					✔			
Reduction of the risk of MI, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE-Is.*							✔	

Abbrv: ACE=angiotensin converting enzyme, LV=left ventricular, MI=myocardial infarction, NYHA=New York Heart Association, SCr=serum creatinine

*Consider using ACE-I first, and, if it is stopped for cough only, consider re-trying the ACE-I after the cough resolves. Use of telmisartan with an ACE-I is not recommended.

#Brand name eprosartan (TEVETEN) is no longer available.

Note: There is evidence that ARBs have smaller blood pressure effects (as monotherapy) in African American patients.

(Prescribing information: ATACAND, 2016; AVAPRO, 2016; BENICAR, 2016; COZAAR, 2015; DIOVAN, 2017; EDARBI, 2016; eprosartan, 2014; MICARDIS, 2014)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials assessing the single entity ARBs in the treatment of hypertension have demonstrated efficacy in lowering systolic (SBP) and diastolic blood pressure (DBP). Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another (Kakio et al, 2017; White et al, 2011; Bakris et al, 2011; Baguet et al, 2006, Oparil et al, 2001; Brunner et al, 2006; Xi et al, 2008; Xu et al, 2012; Conlin et al, 2000). A meta-analysis by Conlin et al found that the absolute weighted-average reductions in SBP and DBP associated with ARB monotherapy were comparable for all ARBs (Conlin et al, 2000). Published literature comparing therapy with ARBs and ACE-Is has generally demonstrated no significant differences between classes (Karlberg et al, 1999; Ruilope et al, 2001; Li et al, 2014). Comparisons of ARBs with other blood pressure lowering agents have not consistently demonstrated superiority of ARBs over other agents from different classes (Flack et al, 2003; Karotsis et al, 2006; Sanders et al, 2011; van Vark et al, 2012).
- Telmisartan is indicated to reduce cardiovascular risk in patients unable to take ACE-Is. The ONTARGET trial compared telmisartan and ramipril monotherapy and in combination with each other and demonstrated no significant difference between any groups in death from cardiovascular causes, MI, stroke or hospitalization for heart failure (ONTARGET Investigators, 2008). The TRANSCEND trial compared telmisartan and placebo and showed no significant difference between groups in death from cardiovascular causes, MI, stroke or heart failure hospitalizations. The composite endpoint of death from cardiovascular causes, MI and stroke occurred in significantly fewer patients in the telmisartan group, but this significance was lost after adjustment for multiplicity of comparisons and overlap with the primary outcome (TRANSCEND Investigators, 2008; Foulquier et al, 2014).
- Losartan is indicated to reduce the risk of stroke in patients with hypertension and LV hypertrophy. The efficacy of losartan was demonstrated in the LIFE trial and its corresponding sub-analyses. Losartan was compared to therapy with atenolol (hydrochlorothiazide could be added to primary regimens if needed for blood pressure control). Results demonstrated a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as compared to atenolol-based regimens (Dahlöf et al, 2002). However, a post-hoc analysis in African American patients showed an increase in the composite of cardiovascular death, MI and stroke in losartan-treated patients compared to atenolol (Julius et al, 2004).
- Candesartan and valsartan are indicated to treat heart failure. Trials demonstrated the efficacy of candesartan alone and in combination with ACE-I therapy compared to placebo in reducing the risk of all-cause mortality, cardiovascular death and/or heart failure hospitalization (Pfeffer et al, 2003a; McMurray et al, 2003; Yusuf et al, 2003). When compared to therapy with enalapril in the RESOLVD trial, candesartan was not significantly better in improving six-minute walking distance, New York Heart Association (NYHA) functional class or quality of life (McKelvie et al, 1999). Losartan has also been evaluated in patients with heart failure and, when compared to captopril, no significant difference was observed in renal function or all-cause mortality (Pitt et al, 1997; Pitt et al, 2000). However, there was a significantly lower risk of sudden death and resuscitated cardiac arrest (Pitt et al, 2000). Trials evaluating the efficacy of valsartan compared to placebo in the Val-HeFT trial show no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, heart failure hospitalizations and morbidity and mortality (Cohn et al, 2001).
- Valsartan is indicated to reduce cardiovascular mortality in patients with post-MI with LV failure or dysfunction. The VALIANT trial compared valsartan with captopril and combination therapy with valsartan plus captopril. No significant differences in all-cause mortality, cardiovascular death, reinfarction or heart failure hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy (Pfeffer et al, 2003b). Losartan has also been evaluated in patients post-MI compared to and in combination with captopril. Results are similar to results observed in the VALIANT trial (Dickstein et al, 2002).
- Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension. However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan and valsartan (Mogensen et al, 2000; Hou et al, 2007; Barnett et al, 2004; Galle et al, 2008; Viberti et al, 2002).
- The ORIENT and ROADMAP studies followed patients with diabetes and compared the effects of olmesartan versus placebo. Outcomes demonstrated a higher rate of death from cardiovascular causes in both trials compared to placebo. This finding contradicts outcomes of other studies that include ARBs and/or olmesartan. A number of factors may have contributed to these outcomes including concomitant medications, patients with higher cardiovascular risks, and other potential confounders. Further studies in diabetic patients are needed to validate findings (Haller et al, 2011; Imai et al, 2011).

- Studies have demonstrated that the combination of two inhibitors of the renin angiotensin-aldosterone system (RAAS), including an ACE-I with an ARB, provides no renal or cardiovascular benefits, and significant adverse events particularly in patients with diabetes and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in the class have safety warnings against combined use (Fried et al, 2013; ONTARGET Investigators, 2008; Parving et al, 2012; Pfeffer et al, 2003b; Sakata et al, 2015).

SAFETY SUMMARY

- All ARBs have a boxed warning that states that use during pregnancy should be avoided. When pregnancy is detected, discontinue the ARB as soon as possible. Drugs that act directly on the renin-angiotensin system (RAS) can cause injury and death to the developing fetus.
- ARB-containing products should not be administered in combination with aliskiren in patients with diabetes mellitus. All ARBs may cause hypotension in volume- or salt-depleted patients and renal impairment.
- Dual blockade of the RAS with ARBs, ACE-Is, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors.
- Other warnings and precautions in certain ARBs include electrolyte abnormalities, hypersensitivity reactions, administration in patients with impaired hepatic function, and sprue-like enteropathy.
- Drug interactions with ARB-containing products include lithium (possible increase in lithium levels) and non-steroidal anti-inflammatory drugs (NSAIDs) (reduce ARB effects and increased risk of renal injury or impairment).
- Common adverse events include hypotension, dizziness, headache, rash, pain, and cough.
- Data from one controlled trial (ROADMAP) and an epidemiologic study (ORIENT) have suggested that high-dose BENICAR (olmesartan 40 mg daily) may increase cardiovascular (CV) risk in diabetic patients, but the overall data are not conclusive (Haller et al, 2011; Imai et al, 2011; FDA Drug Safety Communication: Safety Announcement, 2010; Safety Announcement, 2011; Safety Announcement, 2014).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
ATACAND (candesartan)	Tablet: 4 mg 8 mg 16 mg 32 mg	Heart failure (NYHA class II to IV)†: Tablet: initial, 4 mg daily; target, 32 mg daily Hypertension: Tablet: initial, 16 mg daily when used as monotherapy in patients who are not volume-depleted; maintenance, 8 to 32 mg/day in 1 to 2 divided doses Volume-depleted patients: administer under close medical supervision and consider a lower dose.	Hypertension (children 1 to <6 years of age): Tablet as oral suspension: initial, 0.2 mg/kg daily; maintenance, 0.05 to 0.4 mg/kg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and <50 kg): Tablet: initial, 4 to 8 mg daily; maintenance, 2 to 16 mg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and	Take with or without food. Oral suspension can be prepared from oral tablets.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
			>50 kg): Tablet: initial, 8 to 16 mg daily; maintenance, 4 to 32 mg in 1 to 2 divided doses	
AVAPRO (irbesartan)	Tablet: 75 mg 150 mg 300 mg	Diabetic nephropathy in patients with Type 2 diabetes and hypertension‡: Tablet: target, 300 mg daily in patients who are not volume-depleted Hypertension: Tablet: initial, 150 mg daily; maximum, 300 mg daily Volume or salt-depleted patients: initial, 75 mg daily	Safety and efficacy in children have not been established.	Take with or without food.
BENICAR (olmesartan)	Tablet: 5 mg 20 mg 40 mg	Hypertension: Tablet: initial, 20 mg daily when used as monotherapy in patients who are not volume depleted; maximum, 40 mg daily Volume-depleted patients: administer under close medical supervision and consider a lower dose.	Hypertension (children 6 to 16 years of age and 20 to <35 kg): Tablet: initial, 10 mg daily; maximum, 20 mg daily Hypertension (children 6 to 16 years of age and ≥35 kg): Tablet: initial, 20 mg daily; maximum, 40 mg daily	Take with or without food. Oral suspension can be prepared from oral tablets.
COZAAR (losartan)	Tablet: 25 mg 50 mg 100 mg	Diabetic nephropathy in patients with Type 2 diabetes and hypertension‡: Tablet: initial, 50 mg daily; maintenance, dose should be increased to 100 mg daily based on blood pressure response Hypertension (adult): Tablet: initial, 50 mg	Hypertension (children 6 years of age and older): Tablet: initial, 0.7 mg/kg daily (up to 50 mg total) administered as a tablet or suspension‖	Take with or without food. Oral suspension can be prepared from oral tablets.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
		daily in patients who are not volume-depleted; maintenance, 25 to 100 mg/day in 1 to 2 divided doses Reduction in the risk of stroke in patients with hypertension and LV hypertrophy§: Tablet: initial, 50 mg daily; maintenance, HCTZ 12.5 mg daily should be added and/or the losartan dose increased to 100 mg daily followed by an increase in HCTZ 25 mg daily based on blood pressure response. Volume-depleted patients: 25 mg daily		
DIOVAN (valsartan)	Tablet: 40 mg 80 mg 160 mg 320 mg	Heart failure (NYHA Class II to IV)#: Tablet: initial, 40 mg twice daily; maintenance, uptitration to 80 to 160 mg twice daily should be done to the highest dose as tolerated; maximum, 320 mg in divided doses Hypertension: Tablet: initial, 80 to 160 mg daily when used as monotherapy in patients who are not volume depleted; maintenance, 80 to 320 mg daily Post-myocardial infarction*: Tablet: initial, 20 mg twice daily; target, 160 mg twice daily	Hypertension (children 6 to 16 years of age): Tablet: initial, 1.3 mg/kg daily (up to 40 mg total); maximum, 2.7 mg/kg (up to 160 mg) daily	Take with or without food. Oral suspension can be prepared from oral tablets. Exposure to valsartan with a compounded suspension is 1.6 times greater than with the tablet. If the suspension is replaced by a tablet, then the dose may have to be increased.
EDARBI (azilsartan)	Tablet: 40 mg 80 mg	Hypertension: Tablet: 80 mg daily; consider 40 mg daily for	Safety and efficacy in children have not been	Take with or without food.

Drug	Dosage Form: Strength	Usual Adult Dose	Usual Pediatric Dose	Administration Considerations
		patients on diuretics or volume- or salt-depleted patients.	established.	
MICARDIS (telmisartan)	Tablet: 20 mg 40 mg 80 mg	Cardiovascular risk reduction in patients unable to take ACE-Is: Tablet: initial, 80 mg daily Hypertension: Tablet: initial, 40 mg daily; maximum, 80 mg daily	Safety and efficacy in children have not been established.	Take with or without food.
TEVETEN¥ (eprosartan)	Tablet: 600 mg	Hypertension: Tablet: initial, 600 mg daily when used as monotherapy in patients who are not volume-depleted; maintenance, 400 to 800 mg/day in 1 to 2 divided doses	Safety and efficacy in children have not been established.	Take with or without food.

Abbrv: ACE-I=angiotensin converting enzyme inhibitor, HCTZ=hydrochlorothiazide, LV=left ventricular, NYHA=New York Heart Association
†To reduce the risk of cardiovascular death and heart failure hospitalization in patients with LV systolic dysfunction. Candesartan has an added effect on these outcomes when used with an ACE-I.
‡Reduces the rate of progression to nephropathy in patients with elevated SCr and proteinuria (>300 mg/day).
§There is evidence that this benefit does not apply to African American patients.
‖Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied.
¶ Reduction of risk of myocardial infarction, stroke or cardiovascular death in patients 55 years of age and older at high risk of developing major cardiovascular events. Use of telmisartan with an angiotensin converting enzyme inhibitor is not recommended. Consider using an angiotensin converting enzyme inhibitor first.
#Reduction in heart failure hospitalizations. There is no evidence that valsartan provides added benefit when used with adequate doses of an ACE-I.
*In clinically stable patients with LV failure or dysfunction following myocardial infarction, to reduce the risk of cardiovascular mortality.
¥ Brand name eprosartan (TEVETEN) is no longer available.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ATACAND (candesartan)	No dosage adjustment required in the elderly.	Approved for use in children 1 to <17 years of age for the treatment of hypertension. Children <1 year of age must not receive candesartan. Safety and efficacy in children have not been	No dosage adjustment required.	Initiate with 8 mg once daily for patients with moderate hepatic impairment. No recom-mendations for patients for severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
		established for the treatment of heart failure.			
AVAPRO (irbesartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
BENICAR (olmesartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 years of age and older. Children <1 year of age must not receive olmesartan.	No dosage adjustment required when CrCL is <40 mL/minute.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
COZAAR (losartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 to 16 years of age for hypertension. Not recommended in children <6 years or with GFR <30 mL/min/1.73m^2.	No dosage adjustment required. Children with GFR <30 mL/min/1.73m^2 should not receive losartan as it has not been studied.	The recommended starting dose in mild to moderate hepatic impairment is 25 mg once daily. Not been studied in patients with severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
DIOVAN (valsartan)	No dosage adjustment required in the elderly.	Approved for use in children 6 to 16 years of age for hypertension.	Safety and effectiveness in severe renal impairment (CrCL ≤30 mL/min) have not been established. Children with GFR <30 mL/min/1.73m^2 or those undergoing dialysis should not receive valsartan as it has not been studied.	No dosage adjustment required for mild or moderate hepatic impairment. No dosing recom-mendation for severe hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EDARBI (azilsartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required for mild or moderate hepatic impairment.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
MICARDIS (telmisartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate therapy at a low dose and titrate slowly.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.
TEVETEN[#] (eprosartan)	No dosage adjustment required in the elderly.	Safety and efficacy in children have not been established.	No dosage adjustment required; do not exceed 600 mg daily.	No dosage adjustment required.	Pregnancy Category: D Unknown whether excreted in breast milk; discontinue drug or nursing.

Abbrv: CrCL=creatinine clearance, GFR = glomerular filtration rate
* Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.
[#]Brand name eprosartan (TEVETEN) is no longer available.

CONCLUSION

- The ARBs are FDA-approved to treat hypertension, heart failure, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, cardiovascular risk reduction in patients unable to take ACE-Is, and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.
- Clinical trials assessing the single entity ARBs in the treatment of hypertension have demonstrated efficacy in lowering SBP and DBP. Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another. Published literature have found efficacy with ARB monotherapy is comparable for all ARBs, and in comparison to ACE-Is, ARBs have generally demonstrated no significant differences between classes.
- Evidence-based guidelines recognize the important role ARBs play in the treatment of hypertension and other cardiovascular and renal diseases. There is no consensus on blood pressure goals for certain populations, such as older patients, patients with diabetes, and/or CKD.
- The guidelines also differ on first-line treatment options in various groups, however ARBs are recommended as a first-line option for many patient populations. The current treatment guidelines do not establish a preference for one ARB over another.
    - ACE-Is or ARBs are recommended as a first-line option in patients with CKD with or without proteinuria, due to its renal protective attributes (Go et al, 2013; James et al, 2013; Mancia et al, 2013; Weber et al, 2014).
    - ARBs are also recommended as a first-line option for patients with hypertension complicated by comorbidities, such as cerebrovascular disease (e.g., stroke), vascular diseases, and diabetes (American Diabetes Association, 2017; Go et al, 2013; James et al, 2013; Mancia et al, 2013; Weber et al, 2014; Rosendorff et al, 2015).
    - ARBs are also recommended as a therapy option in those patients who are intolerant to ACE-Is and have heart failure, are post-myocardial infarction, have stable angina and unstable angina/non-ST elevation myocardial infarction, or in cases of left ventricular dysfunction, unless otherwise contraindicated (Amsterdam et al, 2014;

Fihn et al, 2014; Go et al, 2013; O'Gara et al, 2013; Montalescot et al, 2013; Nishimura et al, 2014; Piepoli et al, 2016; Ponikowski et al, 2016; Roffi et al, 2016; Steg et al, 2012; Stout et al, 2016; Weber et al, 2014; Windecker et al, 2014; Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017).

- In black (patients of Caribbean or African descent) hypertensive patients, thiazide-type diuretics or CCBs are generally recommended as first-line therapy, and ARBs may be considered as add-on therapy (James et al, 2013; Weber et al, 2014). However, some guidelines recommend ARBs as a first line treatment option, regardless of race (Go et al, 2013; Rosendorff et al, 2015).
- ARBs are also recommended as a treatment option for patients with coronary artery disease, chronic aortic or mitral regurgitation, and a reasonable option in patients with other cardiac or vascular diseases (Amsterdam et al, 2014; Nishimura et al, 2014; Windecker et al, 2014; Rosendorff et al, 2015).

- Although pharmacokinetic and pharmacodynamic differences exist among ARBs, the clinical relevance of these differences has not been established. Comparative data regarding the ARBs have not demonstrated distinct, clinically significant differences regarding efficacy, safety and tolerability.
- Adverse effects common to all ARBs include hypotension, hyperkalemia, and dizziness (Clinical Pharmacology, 2017).

REFERENCES

- American Diabetes Association. Cardiovascular disease and risk management. Diabetes Care. 2017 Jan;40 Suppl 1:S75-87.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Sep 18. pii: S0735-1097(14)06279-2. doi: 10.1016/j.jacc.2014.09.017.
- ATACAND prescribing information. AstraZeneca LP; Wilmington, DE. July 2016.
- AVAPRO prescribing information. Sanofi-Aventis; New York, NY. July 2016.
- Baguet JP, Nisse-Durgeat S, Mouret S, et al. A placebo-controlled comparison of the efficacy and tolerability of candesartan cilexetil, 8 mg, and losartan, 50 mg, as monotherapy in patients with essential hypertension, using 36-h ambulatory blood pressure monitoring. Int J Clin Pract. 2006 Apr;60(4):391-8.
- Bakris G, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. J Clin Hypertens. 2011;13(2):81-8.
- Barnett AH, Bain SC, Bouter P, et al; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004 Nov 4;351(19):1952-61.
- BENICAR prescribing information. Daiichi Sankyo; Parsippany, NJ. November 2016.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Brunner HR, Arakawa K. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil in achieving 24-hour blood pressure reductions and ambulatory blood pressure goals. Clin Drug Investig. 2006;26(4):185-93.
- Clinical Pharmacology. Elsevier [database on internet]. 2017. Available at: https://www.clinicalkey.com/pharmacology/. Accessed May 26, 2017.
- Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001 Dec 6;345(23):1667-75.
- Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? Am J Hypertens. 2000 Apr;13(4 Pt 1):418-26.
- COZAAR prescribing information. Merck; Whitehouse Station, NJ. December 2015.
- Dahlöf B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet. 2002 Mar 23;359(9311):995-1003.
- Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002 Sep 7;360(9335):752-60.
- DIOVAN prescribing information. Novartis; East Hanover, NJ. February 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 26, 2017.
- EDARBI prescribing information. Takeda Pharmaceuticals America, Inc.; Deerfield, IL. March 2016.
- Eprosartan prescribing information. Mylan Laboratories; Morgantown, WV. November 2014.
- Fihn SD, Blankenship J, Alexander K, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014 Nov 4;64(18):1929-49.
- Flack JM, Oparil S, Pratt JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. J Am Coll Cardiol. 2003;41(7):1148-55.
- Food and Drug Administration (FDA) Drug Safety Communication. FDA Drug Safety Communication: Ongoing safety review of Benicar (olmesartan) and cardiovascular events. [safety announcement]. June 11, 2010. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm215222.htm. Accessed May 26, 2017.
- FDA Drug Safety Communication. FDA Drug Safety Communication: Safety review update of Benicar (olmesartan) and cardiovascular events. [safety announcement]. April 14, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251268.htm. Accessed May 26, 2017.

- FDA Drug Safety Communication. FDA Drug Safety Communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required. [safety announcement]. June 24, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm402323.htm. Accessed May 26, 2017.
- Foulquier S, Böhm M, Schmieder R, et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease subanalysis (TRANSCEND). J Hypertens. 2014;32:1334-41.
- Fried LF, Emanuele N, Zhang JH, et al. Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy (VA NEPHRON-D). N Engl J Med. 2013;369:1892-903.
- Galle J, Schwedhelm E, Pinnetti S, et al for the VIVALDI Investigators. Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. Nephrol Dial Transplant. 2008;23(10):3174-83.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). Hypertension.2014;63(4):878-85.
- Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in Type 2 Diabetes. N Engl J Med 2011;364:907-17.
- Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol. 2007;18:1889-98.
- Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicenter, randomized, placebo-controlled study. Diabetologia. 2011 Dec;54(12):2978-86.
- James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). [Internet]. JAMA. 2014 Feb 5;311(5):507-20.
- Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol. 2004 Mar 17;43(6):1047-55.
- Kakio Y, Uchida HA, Umebayashi R, et al. Practical efficacy of olmesartan versus azilsartan in patients with hypertension: a multicenter randomized-controlled trial (MUSCAT-4 study). Blood Press Monit. 2017 Apr;22(2):59-67.
- Karlberg BE, Lins LE, Hermansson K. Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared to enalapril in elderly patients with primary hypertension. TEES Study Group. J Hypertens. 1999 Feb;17(2):293-302.
- Karotsis AK, Symeonidis A, Mastorantonakis SE, et al. Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. Clin Exp Hypertens. 2006;28(7):655-62.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414.
- Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2014 Aug 22;8:CD009096. doi: 10.1002/14651858.CD009096.pub2.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
- McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation. 1999 Sep 7;100(10):1056-64.
- McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003 Sep 6;362(9386):767-71.
- MICARDIS prescribing information. Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT. December 2014.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed May 26, 2017.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2949-3003.
- Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ. 2000 Dec 9;321(7274):1440-4.
- Nishimura R, Otto C, Bonow R, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185. doi: 10.1016/j.jacc.2014.02.536
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362–e425.
- ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008 Apr 10;358(15):1547-59.
- Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. J Clin Hypertens (Greenwich). 2001 Sep-Oct;3(5):283-91,318.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 26, 2017.
- Parving H, Brenner BM, McMurray JJ, et al. Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes (ALTITUDE). N Engl J Med. 2012 Dec 6;367(32):2204.
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003b Nov 13;349(20):1893-906.
- Pfeffer MA, Swedberg K, Granger CB, et al; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003a Sep 6;362(9386):759-66.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by

representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;27(29):2315-81.
- Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared to captopril on mortality in patients with symptomatic heart failure: randomized trial-the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000 May 6;355(9215):1582-7.
- Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE) Lancet. 1997 Mar 15;349(9054):747-52.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 May 20. pii: ehw128. doi: http://dx.doi.org/10.1093/eurheartj/ehw128
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267-315.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of Hypertension in Patients with Coronary Artery Disease: A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). J Am Coll Cardiol. May 2015;65(18):1998-2038. doi:10.1016/j.jacc.2015.02.038.
- Ruilope L, Jager B, Prichard B. Eprosartan versus enalapril in elderly patients with hypertension: a double-blind, randomized trial. Blood Pressure. 2001;10:223-9.
- Sakata Y, Shiba, Takahashi J, et al. Clinical impacts of additive use of Olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. Eur Heart J. 2015;36(15):915-23.
- Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011.
- SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26; 373(22):2103-16.
- Steg G, James SK, Atar D, et al for Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012. doi:10.1093/eurheartj/ehs215.
- Stout KK, Broberg CS, Book WM, et al. American Heart Association (AHA) Scientific Statement: Chronic Heart Failure in Congenital Heart Disease. Circulation. 2016;133:770-801.
- TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet. 2008;372:1174-83.
- van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012 Aug;33(16):2088-97. doi: 10.1093/eurheartj/ehs075.
- Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002 Aug 6;106(6):672-8.
- Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014 Jan;32(1):3-15.
- White W, Weber M, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57:413-20.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541-619.
- Xi GL, Cheng JW, Lu GC. Meta-analysis of randomized controlled trials comparing telmisartan with losartan in the treatment of patients with hypertension. Am J Hypertens. 2008 May;21(5):546-52.
- Xu FY, Yang B, Shi D, et al. Antihypertensive effects and safety of eprosartan: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2012 Feb;68(2):195-205. doi: 10.1007/s00228-011-1107-3.
- Yancy CW, Jessup M, Bozkurk B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013. DOI: 10.1016/j.jacc.2013.05.020.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Apr 25. doi: 10.1016/j.cardfail.2017.04.014.
- Yusuf S, Pfeffer MA, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003 Sep 6;362(9386):777-81.

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Therapeutic Class Overview
Calcium Channel Blocking Agents (Non-Dihydropyridines)

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (Micromedex® 2.0, 2017; Kannam et al, 2017).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular node (Micromedex 2.0, 2017; Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011; Saseen, 2017).
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (Micromedex 2.0, 2017). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (Micromedex 2.0, 2017; Kannam et al, 2017; Weber et al, 2014).
- The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (Micromedex 2.0, 2017).
- Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017). Caution is also advised in elderly patients (American Geriatrics Society, 2015). Guidelines generally reserve non-dihydropyridine calcium channel blockers for patients with high risk cardiovascular diseases and arrhythmias; therefore, they are usually reserved for progressive cardiovascular and heart disease (American Geriatrics Society, 2015; Amsterdam et al, 2014; Fihn et al, 2014; Go et al, 2014; James et al, 2014; January et al, 2014; KDIGO, 2012; Mancia et al, 2013; Montalescot et al, 2013; Page et al, 2016; Rosendorff et al, 2015; Weber et al, 2014).
- Both the non-dihydropyridine calcium channel blocking agents, diltiazem and verapamil, are available generically in at least 1 formulation (Drugs@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- This review will focus on the non-dihydropyridine calcium channel blocking agents which are Food and Drug Administration (FDA) approved to treat hypertension, atrial fibrillation and flutter, and chronic stable angina. Verapamil is also FDA-approved for unstable angina and variant angina indications. Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. Covera-HS (verapamil extended-release) is not included in this review as it has been discontinued by the manufacturer. This review encompasses all dosage forms, and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Calan (verapamil) tablet	✔
Calan SR (verapamil extended-release) tablet	✔
Cardizem (diltiazem) tablet	✔
Cardizem CD* (diltiazem extended-release) capsule	✔
Cardizem LA† (diltiazem extended-release) tablet	✔
Dilacor XR‡ (diltiazem extended-release) capsule	✔
Tiazac§ (diltiazem extended-release) capsule	✔
Verelan (verapamil sustained-release) capsule	✔
Verelan PM (verapamil extended-release) capsule	✔

*Cartia XT is a branded generic of Cardizem CD.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT is a branded generics of Tiazac.

(*Drugs@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Diltiazem	Verapamil
Angina Pectoris		
Angina due to coronary artery spasm or vasospastic angina	✔ (tablet [Cardizem], extended-release capsule [Cardizem CD])	✔ (Calan)
Chronic stable angina	✔	✔ (Calan)
Unstable angina	-	✔ (Calan)
Arrhythmias		
Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis	-	✔ (Calan)
Prophylaxis of repetitive paroxysmal supraventricular tachycardia	-	✔ (Calan)
Hypertension		
Hypertension	✔ *(with the exception of Cardizem)	-
Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.	✔ *(Cardizem LA)	✔

*May be used alone or in combination with other antihypertensive agents.

(Prescribing Information: CALAN, 2016; CALAN SR, 2016; CARDIZEM, 2016; CARDIZEM CD, 2016; CARDIZEM LA, 2016; DILT-XR, 2012; TIAZAC, 2016; VERELAN, 2016; VERELAN PM, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use (De Rosa et al, 1998; Chugh et al, 2001; van Kesteren et al, 1998; Frishman et al, 1999).

- A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group (De Rosa et al, 1998).

- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medication have not consistently demonstrated "superiority" of either agent (Wright et al, 2004; Rosei et al, 1997).
  - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine (Wright et al, 2004).
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics (Hansson et al, 2000; Pepine et al, 2003; Mancia et al, 2007; Bangalore et al, 2008; Black et al, 2003).

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), or a calcium channel blocker as first-line therapy (Go et al, 2014; James et al, 2013; Mancia et al, 2013; Weber et al, 2014), although the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta blockers as a first-line therapy option (Mancia et al, 2013).
  - In black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy (James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (KDIGO, 2012; Go et al, 2014; James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - There is no consensus on additional populations that calcium channel blockers should be prescribed in. However, other compelling indications that include calcium channel blockers as a first-line treatment option include elderly patients, patients with diabetes, for ventricular rate control in atrial fibrillation, patients with asymptomatic organ damage and asymptomatic atherosclerosis, peripheral artery disease, and metabolic syndrome (Go et al, 2014; James et al, 2014; KDIGO, 2012; Mancia et al, 2013; Weber et al, 2014). A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with coronary artery disease (CAD) who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure (Rosendorff et al, 2015).
  - Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure (Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017).

SAFETY SUMMARY

- Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated

liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.

- In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
- The common adverse effects of diltiazem include bradyarrhythmia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Micromedex 2.0, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Diltiazem	Extended-release capsule: 60 mg 90 mg 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Extended-release tablet: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Tablet: 30 mg 60 mg 90 mg 120 mg	<u>Angina pectoris (chronic stable):</u> Extended-release capsule: initial, 120 or 180 mg once daily; maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) <u>Angina pectoris (due to coronary artery spasm):</u> Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs up to 480 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) <u>Hypertension</u>: Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily	Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Verapamil	Extended-release capsule: 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg Extended-release tablet: 120 mg 180 mg 240 mg Sustained-release capsule: 120 mg 180 mg 240 mg 360 mg Tablet: 40 mg 80 mg 120 mg	Angina pectoris (chronic stable, unstable, and vasospastic): Tablet: maintenance, 80 to 120 mg 3 times daily Arrhythmias: Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day Hypertension: Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to 400 mg once daily; maximum, 400 mg/day Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day	Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug. Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents.

See the current prescribing information for full details

CONCLUSION

- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.
  - Both drugs are available in a generic formulation.
- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure (De Rosa et al, 1998; Chugh et al, 2001; van Kesteren et al, 1998; Frishman et al, 1999; Hauf-Zachariou et al, 1997; Wright et al, 2004; White et al, 2004; Rosei et al, 1997; Ruggenenti et al, 2004; Messerli et al, 2007; Karlberg et al, 2000; Van Bortel et al, 2008; Hilleman et al, 1999; Casas et al, 2005). Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo (Gibson et al, 2000). Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension (Hansson et al, 2000; Pepine et al, 2003; Mancia et al, 2007; Pepine et al, 2006; Bangalore et al, 2008; Brunner et al, 2007; Black et al, 2003).
- There is insufficient evidence to support that one non-dihydropyridine calcium channel blocking agent is safer or more efficacious than another.
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required (Fihn et al, 2012; Fihn et al, 2014; O'Gara et al, 2013; Montalescot et al, 2013). Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is

unsuccessful (Montalescot et al, 2013; Amsterdam et al, 2014). Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates (Montalescot et al, 2013; Amsterdam et al, 2014).

- Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered (January et al, 2014). Propafenone or flecainide ("pill-in-the-pocket") in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease (January et al, 2014). In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended (Zipes et al, 2006; Page et al, 2016). Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation (Page et al, 2016).
- Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure (American Geriatrics Society, 2015).

REFERENCES

- American Geriatrics Society. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-46.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139-228.
- Bangalore S, Messerli F, Cohen J, et al. Verapamil-sustained release-based treatment strategy at reducing cardiovascular events in patients with prior myocardial infarction: an International VErapamil SR-Trandolapril (INVEST) substudy. Am Heart J. 2008;156:241-7.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003;289(16):2073-82.
- Brunner M, Cooper-DeHoff RM, Gong Y, et al; for the INVEST Investigators. Factors influencing blood pressure response to trandolapril add-on therapy in patients taking verapamil SR (from the International Verapamil SR/Trandolapril [INVEST] Study). Am J Cardiol. 2007;99:1549-54.
- CALAN® prescribing information. G.D. Searle, Division of Pfizer, Inc.; New York, NY. October 2016.
- CALAN® SR prescribing information. G.D. Searle, Division of Pfizer, Inc.; New York, NY. October 2016.
- CARDIZEM® prescribing information. Valeant Pharmaceuticals North America, LLC; Bridgewater, NJ. November 2016.
- CARDIZEM® CD prescribing information. Valeant Pharmaceuticals North America, LLC; Bridgewater, NJ. November 2016.
- CARDIZEM® LA prescribing information. Valeant Pharmaceuticals North America, LLC; Bridgewater, NJ. November 2016.
- Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet. 2005 Dec 10;366:2026-33.
- Chugh SK, Digpal K, Hutchinson T, et al. A randomized, double-blind comparison of the efficacy and tolerability of once-daily modified-release diltiazem capsules with once-daily amlodipine tablets in patients with stable angina. J Cardiovasc Pharmacol. 2001 38(3):356-64.
- Clinical Pharmacology online [database on the Internet]. Tampa, FL: Elsevier/Gold Standard; 2017. Available from: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed June 5, 2017.
- De Rosa ML, Giordano A, Melfi M, et al. Antianginal efficacy over 24 hours and exercise hemodynamic effects of once daily sustained-release 300 mg diltiazem and 240 mg verapamil in stable angina pectoris. Int J Cardiol. 1998;63(1):27-35.
- DILT-XR prescribing information. Apotex, Inc; Weston, FL. July 2012.
- Dobesh PP. Stable ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 2, 2017.
- Facts and Comparisons® eAnswers [database on the Internet]. St. Louis, MO: Wolters Kluwer Health, Inc; 2017. Available from: http://online.factsandcomparisons.com. Accessed June 2, 2017.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice

Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354–e471.

- Fihn SD, Blankenship J, Alexander K, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014 Nov 4;64(18):1929-49.
- Frishman WH, Glasser S, Stone P, et al. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol. 1999 Feb 15;83(4):507-14.
- Gibson RS, Hansen JF, Messerli F, et al. Long-term effects of diltiazem and verapamil on mortality and cardiac events in non-Q-wave acute myocardial infarction without pulmonary congestion: post hoc subset analysis of the multicenter diltiazem post infarction trial and the second Danish verapamil infarction trial studies. Am J Cardiol. 2000; 86(3):275-9.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). J Am Coll Cardiol. 2014;63(12):1230-1238.
- Hansson L, Hedner T, Lund-Johansen P, et al. Randomized trial of effects of calcium antagonists compared to diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet. 2000;356(9227):359-65.
- Hauf-Zachariou U, Blackwood RA, Gunawardena KA, et al. Carvedilol vs verapamil in chronic stable angina: a multicentre trial. Eur J Clin Pharmacol. 1997;52(2):95-100.
- Hilleman DE, Ryschon KL, Mohiuddin SM, et al. Fixed-dose combination vs monotherapy in hypertension: a meta-analysis evaluation. J Hum Hypertens. 1999;13:477-83.
- James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
- January CT, Wann LS, Alpert J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Dec 2;64(21):e1-e76.
- Kannam JP, Aroesty JM, Gersh BJ. Calcium-channel blockers in the management of stable angina pectoris. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham, MA: UpToDate; 2017. Available from: https://www.uptodate.com/contents/calcium-channel-blockers-in-the-management-of-stable-angina-pectoris?source=search_result&search=calcium%20channel%20blockers%20angina&selectedTitle=1~150. Accessed June 2, 2017.
- Karlberg BE, Andrup M, Oden A; on behalf of the Swedish Tarka Trialists. Efficacy and safety of a new long-acting drug combination, trandolapril/verapamil as compared to monotherapy in primary hypertension. Blood Pressure. 2000;9:140-5.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414. Available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf. Accessed June 2, 2017.
- Mancia G, Messerli F, Bakris G, et al. Blood Pressure Control and Improved Cardiovascular Outcomes in the International Verapamil SR-Trandolapril Study. Hypertension. 2007;50:299-305.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
- Messerli F, Frishman W, Elliott WJ, et al. Antihypertensive properties of a high-dose combination of trandolapril and verapamil-SR. Blood Press Suppl. 2007;1:6-9.
- Michel T, Hoffmann BB. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollman BC, et al, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill: 2011.
- Micromedex® 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; Updated periodically. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed June 2, 2017.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2949-3003.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol. 2012. doi:10.1016/j.jacc.2012.11.019.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 2, 2017.
- Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. J Am Coll Cardiol. 2016;67(13):e27-115.
- Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the international verapamil-trandolapril study (INVEST): a randomized controlled trial. JAMA. 2003 Dec 3;290(21):2805-16.
- Pepine CJ, Kowey PR, Kupfer S, et al. Predictors of adverse outcome among patients with hypertension and coronary artery disease. J Am Coll Cardiol. 2006;47(3):547-51.
- Rosei EA, Dal Palu C, Leonetti G, et al. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. VHAS Investigators. J Hypertens. 1997;15(11):1337-44.

- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). *J Am Coll Cardiol.* May 2015;65(18):1998-2038.
- Ruggenenti P, Fassi A, Ilieva AP, et al. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. N Engl J Med. 2004 Nov 4;351(19):1941-51.
- Saseen JJ, MacLaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- TIAZAC® prescribing information. Valeant Pharmaceuticals, Inc. Bridgewater, NJ. November 2016.
- Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared to other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs. 2008;8(1):35-44.
- van Kesteren HA, Withagen AJ. A comparative study of once-daily amlodipine vs twice-daily diltiazem controlled-release (CR) in the treatment of stable angina pectoris. Amlodipine Study Group. Cardiovasc Drugs Ther. 1998;12 Suppl 3:233-7.
- VERELAN® prescribing information. Recro Gainesville LLC. Gainesville, GA. November 2016.
- VERELAN® PM prescribing information. Recro Gainesville LLC. Gainesville, GA. November 2016.
- Weber MA, Schiffrin EL, White WB, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014 Jan;32(1):3-15.
- White WB, Lacourciere Y, Gana T, et al. Effects of graded-release diltiazem vs ramipril, dosed at bedtime, on early morning blood pressure, heart rate, and the rate-pressure product. Am Heart J. 2004;148(4):628-34.
- Wright JT Jr, Sica DA, Gana TJ, et al. Antihypertensive efficacy of night-time graded-release diltiazem vs morning amlodipine in African Americans. Am J Hypertens. 2004;17(9):734-42.
- Yancy CW, Jessup M, Bozkurk B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Apr 25. doi: 10.1016/j.cardfail.2017.04.014.
- Zipes D, Camm A, Borggrefe M; ACC/AHA/ESC Committee for Practice Guidelines. American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2006 Sept 5; 48(5):e247-346.

Publication Date: Month DD, YYYY

Therapeutic Class Overview
Calcium Channel Blocking Agents (Dihydropyridines)

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association Heart Disease and Stroke Statistics 2017 update (Benjamin et al, 2017). From 2004 to 2014, mortality associated with cardiovascular disease declined 25.3%.
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (Micromedex® 2.0, 2017; Kannam et al, 2017).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular node (Micromedex 2.0, 2017; Kannam et al, 2017; Dobesh PP, 2017; Michel T, 2011; Saseen, 2017).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (Micromedex 2.0, 2017; Kannam et al, 2017).
- All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects. Guidelines do recommend thiazide-type diuretics or calcium channel blockers in Black hypertensive patients (James et al, 2014; Mancia et al, 2013; Weber et al, 2014). Blood pressure goals for older patients have been a point of debate. The recent SPRINT trial followed patients ≥ 50 years with high blood pressure and increased cardiovascular risks under intense-hypertensive treatment (with a goal of 120 mmHg) compared to standard hypertensive treatment (with a goal of 140 mmHg) over a period of 3.2 years. The trial did end early; however, results demonstrated a reduced primary composite of myocardial infarction (MI), acute coronary syndrome (ACS), stroke, heart failure (HF), or cardiovascular death driven mainly by reduced HF events and cardiovascular death with intense-treatment compared to standard treatment (goal 140 mmHg). SPRINT has pointed to potential clinical benefits associated with a more intensive treatment in certain patients (SPRINT Research Group, 2015).
- Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
- The dihydropyridines are available in a variety of single entity formulations (Micromedex 2.0, 2017; Kannam et al, 2017). All of the single-entity dihydropyridine calcium channel blocking agents are available generically in at least 1 formulation (Drugs@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- Amlodipine is also available in combination with benazepril, perindopril, olmesartan, valsartan, telmisartan, atorvastatin, valsartan/hydrochlorothiazide, or olmesartan/hydrochlorothiazide. However, these combination agents are not included in this review.
- This review will focus on the dihydropyridine calcium channel blocking agents which are Food and Drug Administration (FDA)-approved to treat hypertension and forms of angina, with the exception of nimodipine, which is only FDA-approved for the prophylaxis and treatment of ischemic defects due to vasospasm after a subarachnoid hemorrhage (SAH).

- Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adalat CC (nifedipine extended-release)	✔
Afeditab CR (nifedipine extended-release)*	✔
Amlodipine	✔
Felodipine extended-release	✔
Isradipine	✔
Nicardipine	✔
Nifedipine extended-release	✔
Nimodipine	✔
Nisoldipine extended-release	✔
Norvasc (amlodipine)	✔
Nymalize (nimodipine)	-
Procardia (nifedipine)	✔
Procardia XL (nifedipine extended-release)	✔
Sular (nisoldipine extended-release)	✔

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Angina Pectoris							
Treatment of chronic stable angina	✔ *	-	-	✔ (IR)†	-	-	-
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents	-	-	-	-	✔ (capsule, ER tablet)	-	-
Treatment of vasospastic angina	✔ ‡	-	-	-	✔ (capsule, ER tablet)§	-	-
CAD							
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%	✔	-	-	-	-	-	-
Hypertension							
Treatment of hypertension	✔ ‖	✔ ‖	✔ ¶	✔ ‖	✔ (ER tablet)‖	-	✔ ‖
Treatment of hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions	✔ ‖	✔ ‖	-	-	✔ (ER tablet)‖	-	-
Miscellaneous							

Indication	Amlodipine	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V)	-	-	-	-	-	√	-

*Alone or in combination with other antianginal agents.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. Alone or may be used in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
‖Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.

(Prescribing information: ADALAT CC, 2011; AFEDITAB CR, 2014; felodipine ER, 2014; isradipine, 2014; nicardipine capsule, 2016; nifedipine extended-release, 2016; nimodipine, 2012; nisoldipine extended-release tablet, 2010; NORVASC, 2017; NYMALIZE, 2013; PROCARDIA, 2016; PROCARDIA XL, 2016; SULAR, 2014)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (Koenig, 1997).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established (Sheehy et al, 2000; Van der Krogt et al, 1996; Mounier-Vehier et al, 2002; Kes et al, 2003; Ryuzaki et al, 2007; Saito et al, 2007; Pepine et al, 2003; Whitcomb et al, 2000; White et al, 2003b; Lenz et al, 2001; Drummond et al, 2007; Benetos et al, 2000; Prisant et al, 1995; Mazza et al, 2002; Hollenberg et al, 2003; White et al, 2003a; Jordan et al, 2007; Messerli et al, 2002; Chrysant et al, 2012; Messerli et al, 2000; Jamerson et al, 2004; Neutel et al, 2005; Kuschnir et al, 1996; Chrysant et al, 2007; Chrysant et al, 2004; Fogari et al, 1997; Minami et al, 2007; Hilleman et al, 1999; Jamerson et al, 2007; Malacco et al, 2002; Kereiakes et al, 2007; Tatti et al, 1998; Miranda et al, 2008; Fogari et al, 2007; Ribeiro et al, 2007; Oparil et al, 1996; Chrysant et al, 2008; Chrysant et al, 2009; Oparil et al, 2009; Braun et al, 2009; Littlejohn et al, 2009a; Littlejohn et al, 2009b; Sharma et al, 2007; Neutel et al, 2012; Maciejewski et al, 2006; Ichihara et al, 2006; Karpov et al, 2012; Philipp et al, 2007; Philipp et al, 2011; Schunkert et al, 2009; Ke et al, 2010; Destro et al, 2008; Flack et al, 2009; Schrader et al, 2009; Sinkiewicz et al, 2009; Fogari et al, 2009; Poldermans et al, 2007; Calhoun et al, 2009a; Calhoun et al, 2009b; Crikelair et al, 2009; Pareek et al, 2010; Gustin et al, 1996; Karotsis et al, 2006; Manyemba et al, 1997; Lindholm et al, 2005; Van Bortel et al, 2008; Wiysonge et al, 2007; Baguet et al, 2007).
  - In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (Sheehy et al, 2000; Van der Krogt et al, 1996).
  - The most clinical trial experience has been with amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002; Julius et al, 2004; Zanchetti et al, 2006; Savanitto et al, 1996; Nissen et al, 2004; Ogihara et al, 2008; Jamerson et al, 2008; Weber et al, 2010; Weber et al, 2013; Brown et al, 2000).
- The dihydropyridines have been shown to have favorable effects on cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) in select diseases (Pitt et al, 2000; Dahlöf et al, 2005; Chapman et

al, 2007; Nissen et al, 2004; ALLHAT, 2002; Black et al, 2008; Rahman et al, 2012; Ogihara et al, 2008; Julius et al, 2004; Zanchetti et al, 2006; Jamerson et al, 2008; Bakris et al, 2010; Weber et al, 2010; Weber et al, 2013; Hansson et al, 1999; Borhani et al, 1996; National Intervention Cooperative Study, 1999; Lichtlen et al, 1990; Brown et al, 2000; Estacio et al, 1998).
  - In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002).

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (Go et al, 2014; James et al, 2014; Mancia et al, 2013; Weber et al, 2014). However, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta blockers as a first-line therapy option (Mancia et al, 2013).
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy (James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (KDIGO, 2012; Go et al, 2014; James et al, 2014; Mancia et al, 2013; Weber et al, 2014).
  - In patients with chronic aortic regurgitation (stages B and C), valvular disease, and hypertension, dihydropyridine calcium channel blockers, ACE inhibitors or ARBs are preferred treatment options (Nishimura et al, 2014).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients (Bushnell et al, 2014; Mancia et al, 2013).
  - There is no consensus on additional populations that calcium channel blockers should be prescribed in. However, other compelling indications that include calcium channel blockers as a first-line treatment option include elderly patients, diabetic patients, patients with asymptomatic organ damage and asymptomatic atherosclerosis, peripheral artery disease, and metabolic syndrome (Go et al, 2014; James et al, 2014; KDIGO, 2012; Mancia et al, 2013; Weber et al, 2014). A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina (Rosendorff et al, 2015).
  - The 2013 ESH/ESC guidelines do recommend calcium channel blockers in patients with asymptomatic organ damage and left ventricular (LV) hypertrophy (Mancia et al, 2013). However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure (Ponikowski et al, 2016; Yancy et al, 2013; Yancy et al, 2016; Yancy et al, 2017), although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function (Ponikowski et al, 2016).
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required (Fihn et al, 2012; Fihn et al, 2014; O'Gara et al, 2013; Montalescot et al, 2013). Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful (Montalescot et al, 2013; Amsterdam et al, 2014). Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates (Amsterdam et al, 2014).
- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH (Connolly et al, 2012; Diringer et al, 2011).

SAFETY SUMMARY

- All of the dihydropyridine calcium channel blocking agents are contraindicated in patients with hypersensitivity to any component of the medication. Nicardipine is contraindicated in patients with advanced aortic stenosis. The Adalat CC

formulation of nifedipine is contraindicated in patients with cardiogenic shock and in patients who are concomitantly using strong CYP450 inducers such as rifampin. Nimodipine capsule is contraindicated for concomitant administration with strong CYP3A4 inhibitors such as some macrolide antibiotics, some anti-HIV protease inhibitors, some azole antimycotics and some antidepressants because of risk of significant hypotension.

- Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. As such, nimodipine capsules have a boxed warning against the use of nimodipine capsules for intravenous administration.
- Hypotension may occur occasionally during the initial titration or with dosage increases, and hence, blood pressure should be monitored during initial administration and titration. Dihydropyridines, specifically felodipine and nisoldipine, should be used cautiously in patients with congestive heart failure.
- Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
- Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow as these agents are extensively metabolized by the liver.
- In general, patients should have their blood pressure (with initiation and titration), heart rate and anginal pain monitored. Patients should also be monitored for signs and symptoms of edema.
- (Facts and Comparisons®, 2017; Micromedex 2.0, 2017)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Tablet: 2.5 mg 5 mg 10 mg	Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension: Tablet: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension in children 6 to 17 years of age: Tablet: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.
Felodipine	Extended-release tablet: 2.5 mg 5 mg 10 mg	Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily	Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal
Isradipine	Capsule: 2.5 mg 5 mg	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.
Nicardipine	Capsule:	Angina pectoris (chronic stable):	Allow at least 3 days before

Drug	Available Formulations	Usual Recommended Frequency	Comments
	20 mg 30 mg	Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily	increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).
Nifedipine	Immediate-release capsule: 10 mg 20 mg Extended-release tablet: 30 mg 60 mg 90 mg	Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day	Titration should proceed over a 7- to 14-day period. Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an empty stomach; co-administration with grapefruit juice should be avoided.
Nimodipine	Capsule: 30 mg Oral solution: 60 mg/20 mL	Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days	Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be administered intravenously or by other parenteral routes.
Nisoldipine	Extended-release tablet: 8.5 mg 17 mg 20 mg	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day	Dose adjustments should occur at intervals of not less than 1 week.

Drug	Available Formulations	Usual Recommended Frequency	Comments
	25.5 mg 30 mg 34 mg 40 mg	Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily	Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive peak drug concentration and should be avoided.

See the current prescribing information for full details

CONCLUSION

- The majority of the single entity dihydropyridines are available in a generic formulation, although Nymalize oral solution is the only dihydropyridine formulation available as brand only.
- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented coronary artery disease (CAD). Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.
- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases (Pitt et al, 2000; Dahlöf et al, 2005; Chapman et al, 2007; Nissen et al, 2004; ALLHAT, 2002; Black et al, 2008; Rahman et al, 2012; Ogihara et al, 2008; Julius et al, 2004; Zanchetti et al, 2006; Jaromerson et al, 2008; Bakris et al, 2010; Weber et al, 2010; Weber et al, 2013; Hansson et al, 1999; Borhani et al, 1996; National Intervention Cooperative Study, 1999; Lichtlen et al, 1990; Brown et al, 2000; Estacio et al, 1998). However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002).
- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine (Rahman et al, 2012; Black et al, 2008; ALLHAT, 2002; Julius et al, 2004; Zanchetti et al, 2006; Savanitto et al, 1996; Nissen et al, 2004; Ogihara et al, 2008; Jamerson et al, 2008; Weber et al, 2010; Weber et al, 2013; Brown et al, 2000).

REFERENCES

- ADALAT CC prescribing information. Bayer HealthCare Pharmaceuticals Inc.; Wayne, NJ. April 2011.
- AFEDITAB CR prescribing information. Actavis Pharma, Inc. Parsippany, NJ. September 2014.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium-channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002 Dec 18;288(23):2981-97.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139-228.
- Baguet JP, Legallicier B, Auquier P, et al. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. Clin Drug Investig. 2007;27(11):735-53.

- Bakris GL, Sarafidis PA, Weir MR, et al. ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. Lancet. 2010 Apr 3;375(9721):1173-81.
- Benetos A, Consoli S, Safavian A, et al. Efficacy, safety, and effects on quality of life of bisoprolol/hydrochlorothiazide vs amlodipine in elderly patients with systolic hypertension. Am Heart J. 2000 Oct;140(4):E11.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.
- Black HR, Davis B, Barzilay J, et al. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care. 2008 Feb;31(2):353-60.
- Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. JAMA. 1996;276:785-791.
- Braun N, Ulmer HJ, Handrock R, et al. Efficacy and safety of the single pill combination of amlodipine 10 mg plus valsartan 160 mg in hypertensive patients not controlled by amlodipine 10 mg plus olmesartan 20 mg in free combination (abstract). Curr Med Res Opin. 2009;25(2):421-30.
- Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the international nifedipine GTS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000; 356:366-72.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45(5):1545-88.
- Calhoun D, Crikelair N, Yen J, et al. Amlodipine/valsartan/hydrochlorothiazide triple combination therapy in moderate/severe hypertension: secondary analyses evaluating efficacy and safety. Adv Ther. 2009a;26(11):1012-23.
- Calhoun DA, Lacourciere Y, Chiang YT, et al. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized controlled trial. Hypertension. 2009b;54:32-9.
- Chapman N, Dobson J, Wilson S, et al. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007 Apr;49(4):839-45.
- Chrysant SG. Blood pressure effects of high-dose amlodipine-benazepril combination in black and white hypertensive patients not controlled on monotherapy. Drugs RD. 2012;12(2):57-64.
- Chrysant SG, Bakris GL. Amlodipine/benazepril combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. Am J Hypertens. 2004 Jul;17(7):590-6.
- Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther. 2008 Apr;30(4):587-604.
- Chrysant SG, Oparil S, Melino M, et al. Efficacy and safety of long-term treatment with the combination of amlodipine besylate and olmesartan medoxomil in patients with hypertension. J Clin Hypertens (Greenwich). 2009;11:475-82.
- Chrysant SG, Sugimoto DH, Lefkowitz M, et al. The effects of high-dose amlodipine/benazepril combination therapies on blood pressure reduction in patients not adequately controlled with amlodipine monotherapy. Blood Press Suppl. 2007 Mar;1:10-7.
- Clinical Pharmacology online [database on the Internet]. Tampa, FL: Elsevier/Gold Standard; 2017. Available from: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed June 5, 2017.
- Connolly ES, Rabinstein AA, Carhuapoma R, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage; a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012 Jun;43(6):1711-1737.
- Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required vs atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet. 2005 Sep 10-16;366(9489):895-906.
- Destro M, Luckow A, Samson M, et al. Efficacy and safety of amlodipine/valsartan compared to amlodipine monotherapy in patients with stage 2 hypertension: a randomized, double-blind, multicenter study: the EX-EFFeCTS study. J Am Society Hypertension. 2008;2:294-302.
- Diringer MN, Bleck TP, Menon D, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011 Sep;15 (2):211-40.
- Dobesh PP. Stable ischemic heart disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 5, 2017.
- Drummond W, Munger M, Essop M, et al. Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. J Clin Hypertens. 2007;9:742-50.
- Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: implications of the appropriate blood pressure control in diabetes (ABCD) trial. Am J Cardiol. 1998;82(9B):9R-14R.
- Facts and Comparisons® eAnswers [database on the Internet]. St. Louis, MO: Wolters Kluwer Health, Inc.; 2017. Available from: http://online.factsandcomparisons.com. Accessed June 5, 2017.
- Felodipine ER prescribing information. Glenmark Generics Ltd. Mahwah, NJ. December 2014.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice

Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354–e471.

- Fihn SD, Blankenship J, Alexander K, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014 Nov 4;64(18):1929-49.
- Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared to amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. J Hum Hypertens. 2009;23:479-89.
- Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. J Cardiovasc Pharmacol. 1997 Oct;30(4):497-503.
- Fogari R, Mugellini A, Derosa G; CANDIA (CANdesartan and DIuretic vs Amlodipine in hypertensive patients) Study Group. Efficacy and tolerability of candesartan cilexetil/hydrochlorothiazide and amlodipine in patients with poorly controlled mild-to-moderate essential hypertension. J Renin Angiotensin Aldosterone Syst. 2007 Sep;8(3):139-44.
- Fogari R, Zoppi A, Mugellini A, et al. Efficacy and safety of two treatment combinations of hypertension in very elderly patients. Archives of Gerontology and Geriatrics. 2009;48:401-5.
- Gustin G, White WB, Taylor S, et al. Clinical outcome of a mandatory formulary switch for dihydropyridine calcium-channel blocker therapy at a Veteran's Administration Medical Center. Am J Hypertens. 1996;9(4 Pt 1):312-6.
- Hansson L, Lindholm LH, Ekbom T, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999 Nov 20;354(9192):1751-6.
- Hilleman DE, Ryschon KL, Mohiuddin SM, et al. Fixed-dose combination vs monotherapy in hypertension: a meta-analysis evaluation. J Hum Hypertens. 1999;13:477-83.
- Hollenberg HK, Williams GH, Anderson R, et al. Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium-channel blocking agent in patients with systolic hypertension. Arch Intern Med. 2003;163(13):1543-8.
- Ichihara A, Kaneshiro Y, Takemitsu T, et al. Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients. J Hum Hypertens. 2006 Oct;20(10):787-94.
- Isradipine prescribing information. Actavis Pharma, Inc. Parsippany, NJ. June 2014.
- Jamerson K, Bakris GL, Dahlöf B, et al; for the ACCOMPLISH Investigators. Exceptional early blood pressure control rates: the ACCOMPLISH trial. Blood Press. 2007;16(2):80-6.
- Jamerson KA, Nwose O, Jean-Louis L, et al. Initial angiotensin-converting enzyme inhibitor/calcium-channel blocker combination therapy achieves superior blood pressure control compared to calcium-channel blocker monotherapy in patients with stage 2 hypertension. Am J Hypertens. 2004 Jun;17(6):495-501.
- Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. N Engl J Med. 2008;359:2417-28.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20.
- Jordan J, Engeli S, Boye SW, et al. Direct renin inhibition with aliskiren in obese patients with arterial hypertension. Hypertension. 2007 May;49:1047-55.
- Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004 Jun 19;363(9426):2022-31.
- Kannam JP, Aroesty JM, Gersh BJ. Calcium-channel blockers in the management of stable angina pectoris. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017. Available from: http://www.uptodate.com/contents/calcium-channel-blockers-in-the-management-of-stable-angina-pectoris?source=search_result&search=angina&selectedTitle=6~150. Accessed June 5, 2017.
- Karotsis AK, Symeonidis A, Mastorantonakis SE, et al. Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. Clin Exp Hypertens. 2006;28(7):655-62.
- Karpov Y, Dongre N, Vigdorchik A, et al. Amlodipine/valsartan single-pill combination: a prospective, observational evaluation of the real-life safety and effectiveness in the routine treatment of hypertension. Adv Ther. 2012;29(2):134-147.
- Ke Y, Zhu D, Hong H, et al. Efficacy and safety of a single-pill combination of amlodipine/valsartan in Asian hypertensive patients inadequately controlled with amlodipine monotherapy. Curr Med Res Opin. 2010;26:1705-13.
- Kereiakes DJ, Neutel JM, Punzi HA, et al. Efficacy and safety of olmesartan medoxomil and hydrochlorothiazide compared to benazepril and amlodipine besylate. Am J Cardiovasc Drugs. 2007;7(5):361-72.
- Kes S, Caglar N, Canberk A, et al. Treatment of mild-to-moderate hypertension with calcium-channel blockers: a multicentre comparison of once-daily nifedipine GITS with once-daily amlodipine. Curr Med Res Opin. 2003; 19(3):226-37.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414.
- Koenig W, Hoher M. Felodipine and amlodipine in stable angina pectoris: results of a randomized double-blind crossover trial. J Cardiovasc Pharmacol. 1997;29(4):520-4.
- Kuschnir E, Acuña E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared to amlodipine 5 mg, benazepril 20 mg, and placebo. Clin Ther. 1996;18(6):1213-24.
- Lenz TL, Wurdeman RL, Hilleman DE. Comparison of 24-hour blood pressure profiles in patients with hypertension who were switched from amlodipine to nisoldipine. Pharmacotherapy. 2001;21(8):898-903.

- Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of coronary artery disease in humans by the calcium-channel blocker nifedipine: results of the INTACT study (International Nifedipine Trial on Antiatherosclerotic Therapy). Cardiovasc Drugs Ther. 1990 Aug;4 Suppl 5:1047-68.
- Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53.
- Littlejohn TW 3rd, Majul CR, Olvera R, et al. Telmisartan plus amlodipine in patients with moderate or severe hypertension: results from a subgroup analysis of a randomized, placebo-controlled, parallel-group, 4x4 factorial study. Postgrad Med. 2009a Mar;121(2):5-14.
- Littlejohn TW 3rd, Majul CR, Olvera R, et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich). 2009b Apr;11(4):207-13. .
- Maciejewski S, Mohiuddin SM, Packard KA, et al. Randomized, double-blind, crossover comparison of amlodipine and valsartan in African-Americans with hypertension using 24-hour ambulatory blood pressure monitoring. Pharmacotherapy. 2006 Jul;26(7):889-95.
- Malacco E, Piazza S, Carretta R, et al; Italian Blood Pressure Study Group. Comparison of benazepril-amlodipine and captopril-thiazide combinations in the management of mild-to-moderate hypertension. Int J Clin Pharmacol Ther. 2002 Jun;40(6):263-9.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
- Manyemba J. A randomized crossover comparison of reserpine and sustained-release nifedipine in hypertension. Cent Afr J Med. 1997 Dec;43(12):344-9.
- Mazza A, Gil-Extremera B, Maldonato A, et al. Nebivolol vs amlodipine as first-line treatment of essential arterial hypertension in the elderly. Blood Press. 2002;11(3):182-8.
- Medispan PriceRx [internet database]. Updated periodically. Available by subscription at: https://pricerx.medispan.com. Accessed June 5, 2017.
- Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) vs high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol. 2000 Dec 1;86:1182-7.
- Messerli FH, Weir MR, Neutel JM. Combination therapy of amlodipine and benazepril vs monotherapy of amlodipine in a practice-based setting. Am J Hypertens. 2002 Jun;15(6):550-6.
- Michel T, Hoffmann BB. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollman BC, et al, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill: 2011.
- Micromedex 2.0 [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; Updated periodically. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed June 5, 2017.
- Minami J, Abe C, Akashiba A, et al. Long-term efficacy of combination therapy with losartan and low-dose hydrochlorothiazide in patients with uncontrolled hypertension. Int Heart J. 2007 Mar;48(2):177-86.
- Miranda RD, Mion D, Rocha JC, et al. An 18-week, prospective, randomized, double-blind, multicenter study of amlodipine/ramipril combination vs amlodipine monotherapy in the treatment of hypertension: the assessment of combination therapy of amlodipine/ramipril (ATAR) study. Clin Ther. 2008;30:1618-28.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2949-3003.
- Mounier-Vehier C, Jaboureck O, Emeriau JP, et al. Randomized, comparative, double-blind study of amlodipine vs nicardipine as a treatment of isolated systolic hypertension in the elderly. Fundam Clin Pharmacol. 2002;16(6):537-44.
- National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension. 1999 Nov;34(5):1129-33.
- Neutel JM, Mancia G, Black HR, et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012 Apr;14(4):206-215.
- Neutel JM, Smith DH, Weber MA, et al. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. J Clin Hypertens. 2005 Nov;7(11):641-6.
- Nicardipine capsule prescribing information. Mylan Pharmaceuticals, Inc. Morgantown, WV. September 2016.
- Nifedipine extended-release prescribing information. Oceanside Pharmaceuticals. Bridgewater, NJ. June 2016.
- Nimodipine prescribing information. Caraco Pharmaceutical Laboratories, Ltd.; Detroit, MI. January 2012.
- Nishimura R, Otto C, Bonow R, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185.
- Nisoldipine extended-release tablet prescribing information. Mylan Pharmaceuticals Inc.; Morgantown, WV. January 2010.
- Nissen SE, Tuzcu EM, Libby P, et al; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292(18):2217-25.
- NORVASC prescribing information. Pfizer Inc.; New York, NY. March 2017.
- NYMALIZE prescribing information. Arbor Pharmaceuticals Inc.; Atlanta, GA. March 2017.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol. 2012. doi:10.1016/j.jacc.2012.11.019.

- Ogihara T, Nakao K, Fukui T, et al; Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared to amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension. 2008 Feb;51(2):393-8.
- Oparil S, Barr E, Elkins M, et al. Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, vs amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension. Clin Ther. 1996 Jul-Aug;18(4):608-25.
- Oparil S, Lee J, Karki S, et al. Subgroup analyses of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartan medoxomil: evaluation by baseline hypertension stage and prior antihypertensive medication use. J Cardiovasc Pharmacol. 2009;54(5):427-36.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD : Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/. Accessed on June 5, 2017.
- Pareek A, Salkar H, Mulay P, et al. A randomized, comparative, multicenter, evaluation of atenolol/amlodipine combination with atenolol alone in essential hypertension patients. Am J Ther. 2010;17:46-52.
- Pepine CJ, Cooper-DeHoff RM, Weiss RJ, et al. Comparative Efficacy and Safety of Nisoldipine and Amlodipine (CESNA-II) Study Investigators. Comparison of effects of nisoldipine-extended-release and amlodipine in patients with systemic hypertension and chronic stable angina pectoris. Am J Cardiol. 2003; 91(3):274-9.
- Philipp T, Glazer RD, Wernsing M, et al. Initial combination therapy with amlodipine/valsartan compared to monotherapy in the treatment of hypertension (abstract). J Amer Soc Hypertens. 2011;5(5):417-424.
- Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007 Apr;29(4):563-80.
- Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation. 2000;102(13):1503-10.
- Poldermans D, Glazes R, Kargiannis S, et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared to lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. Clin Ther. 2007 Feb;29(2):279-89.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129-2200.
- Prisant LM, Weir MR, Papademetriou V, et al. Low-dose combination therapy: an alternative first-line approach to hypertension treatment. Am Heart J. 1995 Aug;130(2):359-66.
- PROCARDIA prescribing information. Pfizer Inc.; New York, NY. July 2016.
- PROCARDIA XL prescribing information. Pfizer Inc.; New York, NY. July 2016.
- Rahman M, Ford CE, Cutler JA, et al. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. Clin J Am Soc Nephrol. 2012;7:989-1002.
- Ribeiro AB, Mion D Jr, Marin MJ, et al; Latin American Hypertension Study (LAMHYST) Group. Antihypertensive efficacy of amlodipine and losartan after two 'missed' doses in patients with mild to moderate essential hypertension. J Int Med Res. 2007 Nov-Dec;35(6):762-72.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). J Am Coll Cardiol. 2015;65(18):1998-2038. doi:10.1016/j.jacc.2015.02.038.
- Ryuzaki M, Nakamoto H, Nishida E, et al. Crossover study of amlodipine vs nifedipine CR with home blood pressure monitoring via cellular phone: internet-mediated open-label crossover trial of calcium-channel blockers for hypertension (I-TECHO trial). J Hypertens. 2007 Nov;25(11):2352-8.
- Saito I, Saruta T. Controlled release nifedipine and valsartan combination therapy in patients with essential hypertension: The Adalat CR and valsartan cost-effectiveness combination (ADVANCE-Combi) study. J Hypertens. 2007 Nov;25(11):2352-8.
- Saseen JJ, MacLaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 10th edition. New York (NY): McGraw-Hill; 2017.
- Schrader J, Salvetti A, Calvo C, et al. The combination of amlodipine/valsartan 5/160 mg produces less peripheral oedema than amlodipine 10 mg in hypertensive patients not adequately controlled with amlodipine 5 mg. Int J Clin Pract. 2009;63:217-25.
- Schunkert H, Glazer RD, Wernsing M, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on amlodipine monotherapy. Curr Med Res Opin. 2009;25:2655-62.
- Sharma A, Bagchi A, Kinagi SB, et al. Results of a comparative, phase III, 12-week, multicenter, prospective, randomized, double-blind assessment of the efficacy and tolerability of a fixed-dose combination of telmisartan and amlodipine vs amlodipine monotherapy in Indian adults with stage II hypertension. Clin Ther. 2007;29:2667-76.
- Sheehy O, LeLorier J. Patterns of amlodipine and felodipine use in an elderly Quebec population. Can J Cardiol. 2000;16(9):1109-17.
- Sinkiewicz W, Glazer RD, Kavoliuniene A, et al. Efficacy and tolerability of amlodipine/valsartan combination therapy in hypertensive patients not adequately controlled on valsartan monotherapy. Curr Med Res Opin. 2009;25:315-24.
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015 Nov 26; 373(22):2103-16.
- SULAR prescribing information. Shionogi Inc.; Florham Park, NJ. March 2014.
- Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril vs Amlodipine Cardiovascular Events Trial (FACET) in patients with hypertension and non-insulin dependent diabetes mellitus. Diabetes Care. 1998; 21:597-603.
- Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared to other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs. 2008;8(1):35-44.

- Van Der Krogt J, Brand R, Dawson E. Amlodipine vs extended-release felodipine in general practice: A randomized, parallel-group study in patients with mild-to-moderate hypertension. Curr Therap Res. 1996; 57 (3):145-58.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). J Hypertens. 2014 Jan;32(1):3-15.
- Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol. 2010 Jun 29;56(1):77-85.
- Weber MA, Jamerson K, Bakris G, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. Lancet. 2013;381:537-45.
- Whitcomb C, Enzmann G, Pershadsingh HA, et al. A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension. Int J Clin Pract. 2000;54(8):509-13.
- White WB, Duprez D, St Hillaire R, et al. Effects of the selective aldosterone blocker eplerenone vs the calcium antagonist amlodipine in systolic hypertension. Hypertension. 2003a;41(5):1021-6.
- White WB, Saunders E, Noveck RJ, et al. Comparative efficacy and safety of nisoldipine extended-release (ER) and amlodipine (CESNA-III study) in African American patients with hypertension. Am J Hypertens. 2003b;16(9 Pt 1):739-45.
- Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD002003. doi: 10.1002/14651858.CD002003.pub2.
- Yancy CW, Jessup M, Bozkurk B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.
- Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017 Apr 25. doi: 10.1016/j.cardfail.2017.04.014.
- Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J Hypertens. 2006 Nov;24(11):2163-8.

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Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (Buckley et al, 2013; Wu et al, 2013).
  - PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest. Normal pulmonary arterial systolic pressure ranges from 15 to 30 mmHg, diastolic pressure from 4 to 12 mmHg, and normal mPAP is ≤20 mmHg (UptoDate, 2016).
  - PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (Gomberg-Maitland et al, 2011).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (Buckley et al, 2013).
- The World Health Organization (WHO) classifies PH into 5 groups:
  - Group 1 – PAH
  - Group 2 – PH owing to heart disease
  - Group 3 – PH owing to lung diseases and/or hypoxia
  - Group 4 – Chronic thromboembolic PH (CTEPH)
  - Group 5 – PH with unclear or multifactorial etiologies
- WHO Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (Simonneau et al, 2013).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (Stringham et al, 2010):
  - Class I: No limitation of physical activity
  - Class II: Slight limitation of physical activity
  - Class III: Marked limitation of physical activity
  - Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at seven to 26 cases per million adults (Pogue et al, 2016). The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy (McLaughlin et al, 2009). The median survival in the 1980s was 2.8 years; this has improved to seven years in the late 2000s (Pogue et al, 2016).
- CTEPH (WHO Group 4) is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - The incidence of CTEPH is uncertain, but it occurs in up to 4% of patients after an acute pulmonary embolism (Simonneau et al, 2009).
- Specific agents to treat PAH primarily target three pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (Wu et al, 2013). There are currently 10 molecular entities within five therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (Facts and Comparisons, 2017).
  - Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral selexipag).
  - Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).
- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (McLaughlin et al, 2009).
- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test.

Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (Galiè et al, 2015[b]; McLaughlin et al, 2009; Taichman et al, 2014).

- For patients who do not have a positive acute vasodilator response to testing and are considered low to moderate risk based on clinical assessment, oral mono- or combination therapy with certain agents are recommended. These include ERAs, PDE-5 inhibitors, an sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Combination therapy may be considered if patients are not responding adequately to monotherapy or are not candidates for monotherapy (Barst, 2009; Galiè et al, 2015[b]; McLaughlin et al, 2009; Taichman et al, 2014).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (McLaughlin et al, 2009).
- ADEMPAS (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. ADEMPAS (riociguat) has the additional FDA approval for treating adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH. ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (Archer, 2013).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (McLaughlin et al, 2009). PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (Asaki et al, 2015). ORENITRAM (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (REMODULIN and TYVASO). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (McLaughlin et al, 2009). Among these agents, epoprostenol IV is the only agent which has demonstrated improved patient survival in high risk PAH patients (Galiè et al, 2015[b]). UPTRAVI (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. ORENITRAM and UPTRAVI are the only orally administered agents that work within the prostacyclin pathway (Asaki et al, 2015).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (LETAIRIS [ambrisentan], OPSUMIT [macitentan], and TRACLEER [bosentan]) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (McLaughlin et al, 2009).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, REVATIO (sildenafil) and ADCIRCA (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ERAs			
LETAIRIS (ambrisentan)	Gilead	06/15/2007	-
OPSUMIT (macitentan)	Actelion	10/18/2013	-
TRACLEER (bosentan)	Actelion	11/20/2001	-
PDE-5 inhibitors			
ADCIRCA (tadalafil)	Eli Lilly	05/22/2009	-
REVATIO (sildenafil)	Pfizer	06/03/2005	✔ *
Prostacyclin receptor agonist			
UPTRAVI (selexipag)	Actelion Pharmaceuticals	12/21/2015	-
PCAs			
FLOLAN (epoprostenol)	GlaxoSmithKline	4/14/2000	✔
VELETRI (epoprostenol)	Actelion Pharmaceuticals	8/25/2010	-
ORENITRAM (treprostinil)	United Therapeutics	12/20/2013	-
REMODULIN (treprostinil)	United Therapeutics	5/21/2002	-
TYVASO (treprostinil)	United Therapeutics	7/30/2009	-
VENTAVIS (iloprost)	Actelion Pharmaceuticals	12/29/2004	-
sGC stimulator			
ADEMPAS (riociguat)	Bayer Healthcare	10/08/2013	-

*REVATIO tablet and IV formulations are currently available generically; however, the oral suspension is brand-only.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-approved Indications

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (ioprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability	✔ ¶		✔ ≠			✔ ¶¶	✔ ₴			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay disease progression and reduce hospitalization					✔ **						✔ ‡		
Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											✔ ¥

Indication	ADCIRCA (tadalafil)	ADEMPAS (riociguat)	FLOLAN (epoprostenol)	LETAIRIS (ambrisentan)	OPSUMIT (macitentan)	ORENITRAM (treprostinil)	REMODULIN (treprostinil)	REVATIO (sildenafil)	TRACLEER (bosentan)	TYVASO (treprostinil)	UPTRAVI (selexipag)	VELETRI (epoprostenol)	VENTAVIS (ioprost)
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with ADCIRCA to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									

Abbrv: NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization, CTEPH=chronic thromboembolic pulmonary hypertension

*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (60%) or PAH associated with connective tissue diseases (34%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies included predominantly WHO FC II to III. Patients had idiopathic PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital systemic-to-pulmonary shunts (10%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

¥Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

ΩStudies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

₳Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

≠Studies included predominately patients with NYHA class III or IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with connective tissue diseases (19%), and PAH associated with congenital systemic-to-pulmonary shunts (23%).** Disease progression included death, initiation of IV or SC prostacyclin vasodilators, or clinical worsening of PAH (decreased 6-minute walk distance (6MWD), worsened PAH symptoms, and need for additional PAH treatment).

¶¶The study that established effectiveness included predominantly patients with WHO FC II and III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, ORENITRAM has not been shown to add to other vasodilator therapy.

(Prescribing information: ADCIRCA, 2017; ADEMPAS, 2017; FLOLAN, 2016; LETAIRIS, 2015; OPSUMIT, 2017; ORENITRAM, 2017; REMODULIN, 2014; REVATIO, 2015; TRACLEER, 2016; TYVASO, 2016; UPTRAVI, 2015; VELETRI, 2016; VENTAVIS, 2013)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

ADCIRCA (tadalafil)

- ADCIRCA was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO FC II or III symptoms. Treatment with ADCIRCA significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo (Galiè et al, 2009). In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO FC compared to baseline of the PHIRST trial (Oudiz et al, 2012).

ADEMPAS (riociguat)

- The efficacy and safety of ADEMPAS were evaluated in CHEST-1, a multinational, multicenter, double-blind, 16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week two. At week 16, the placebo adjusted mean increase in 6MWD within the ADEMPAS group was 46 m (95% confidence interval [CI], 25 m to 67 m; P<0.001) (Ghofrani et al, 2013[a]).
    - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an eight-week, double-blind dose-adjustment phase, followed by an open-label study phase that continued until ADEMPAS received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over one year of treatment. The safety profile of ADEMPAS in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to one year in CHEST-2. In the observed population at one year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n=172) versus CHEST-1 baseline (n=237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n=176) versus CHEST-1 baseline (n=236). Of patients treated for one year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (eight [5%] were receiving ERAs and four [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at one year (Simmoneau et al, 2015). An exploratory analysis noted a significant association with overall survival for 6MWD and NT-proBNP concentration at baseline (P=0.0199, and 0.0183, respectively), and at follow-up (P=0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At two years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (Simonneau et al, 2016). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.
- The efficacy and safety of ADEMPAS were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR >300 dyn*sec*cm^{-5} and a PAP_{mean} >25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to one of three treatment groups: placebo (n=126), an exploratory capped titration arm of ADEMPAS 1.5 mg three times daily (n=63), or a capped maximum dose of ADEMPAS 2.5 mg three times daily (n=254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the ADEMPAS 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the ADEMPAS 2.5 mg treatment group was 36 m (95% CI, 20 m to 52 m, P<0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (Ghofrani et al, 2013[b]).
    - An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an eight-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received ADEMPAS monotherapy and 199 received ADEMPAS in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term ADEMPAS treatment. Assessments took place at entry to PATENT-2, at weeks two, four, six, eight, and 12, and every three months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received one year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al, 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC

at baseline (P=0.0006, 0.0225, and 0.0191, respectively), and at follow-up (P=0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at one year and 79% (95% CI, 74 to 82%) at two years (Ghofrani et al, 2016). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.

FLOLAN (epoprostenol)

- The safety and efficacy of chronically-infused FLOLAN were evaluated in two similar, open-label, randomized trials of eight to12 weeks' duration comparing FLOLAN plus conventional therapy (eg. anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (N=106). The average FLOLAN dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving FLOLAN plus conventional therapy for eight to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week one. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.
- The efficacy of chronically-infused FLOLAN in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized,12-week trial (N=111) comparing FLOLAN plus conventional therapy with conventional therapy alone. The mean FLOLAN dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous FLOLAN plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with FLOLAN plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the FLOLAN plus conventional therapy group and 27% of conventional therapy group alone worsening.

LETAIRIS (ambrisentan)

- The safety and efficacy of LETAIRIS in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared LETAIRIS to placebo in 394 patients. Compared to placebo, treatment with LETAIRIS resulted in a significant increase in exercise capacity as measured by 6MWD (Galiè et al, 2008). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg LETAIRIS groups (25, 28 and 37 m, respectively). After two years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (Oudiz et al, 2009).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of LETAIRIS in patients with PH receiving LETAIRIS 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (Badesch et al, 2012).
- The AMBITION trial (n=610) was a double-blind, randomized, Phase 3/4 trial which compared combination treatment with LETAIRIS plus ADCIRCA to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs. monotherapy groups (P=0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs. pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; P<0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (Galiè et al, 2015[a]). Based on results from the AMBITION trial, the FDA-

approved LETAIRIS in combination with ADCIRCA to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

OPSUMIT (macitentan)

- The efficacy and safety of OPSUMIT on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the three month period prior to randomization. Patients were randomized to placebo (n=250), OPSUMIT 3 mg once daily (n=250), or OPSUMIT 10 mg once daily (n=242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, OPSUMIT 3 mg, and OPSUMIT 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus seven days. Pre-specified secondary endpoints included change from baseline to month six in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, OPSUMIT 3 mg, and OPSUMIT 10 mg groups, respectively. OPSUMIT 10 mg once daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; P<0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of OPSUMIT 10 mg was primarily due to its reduction in clinical worsening (Pulido et al, 2013).
    - In a sub-group analysis of the effect of OPSUMIT on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, OPSUMIT 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with OPSUMIT 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; P=0.1208) and with OPSUMIT 10 mg by 32.3% (HR, 0.677; 95% CI, 0.514 to 0.891; P=0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the OPSUMIT 3 mg group (P=0.0004) and by 49.8% in the OPSUMIT 10 mg group (P<0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the OPSUMIT 3 mg arm (P=0.0001) and by 52.3% in the OPSUMIT 10 mg arm (P=0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (Channick et al, 2015).

REMODULIN (treprostinil)

- The safety and efficacy of REMODULIN were evaluated in two identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. REMODULIN was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on REMODULIN was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. The Borg dyspnea score was significantly improved by REMODULIN during the 6-minute walk test. REMODULIN also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

ORENITRAM (treprostinil)

- The efficacy and safety of ORENITRAM were evaluated in three multi-center, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
    - FREEDOM-M compared twice daily administration of ORENITRAM with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The ORENITRAM group showed a significant improvement in 6MWD of 23 m (P=0.0125). More than 50% of patients had an improvement of ≥20 m, and over 30% of patients had an improvement of >50 m (Jing et al, 2013). ORENITRAM demonstrated AEs typical of prostacyclin treatments (Waxman, 2013).
    - FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (Tapson et al, 2012; Tapson et al, 2013).

REVATIO (sildenafil)

- The safety and efficacy of REVATIO were evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO FC II or III symptoms. Compared to placebo, REVATIO significantly improved exercise capacity, as measured by the 6MWD, WHO FC symptoms and hemodynamics (Galiè et al, 2005). In a three-year extension study (SUPER-2), 46% of patients increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline, 19% had died and 17% discontinued treatment or were lost to follow-up (Rubin et al, 2011). The addition of REVATIO to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. REVATIO added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (Simonneau et al, 2008).

TRACLEER (bosentan)

- TRACLEER was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from two randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all TRACLEER groups compared to placebo. TRACLEER was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (Channick et al, 2001; Rubin et al, 2002). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with TRACLEER resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the TRACLEER group compared to placebo (Galiè et al, 2008[b]; McLaughlin et al, 2006).
    - The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term TRACLEER therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (Simmoneau et al, 2014).
- The COMPASS-2 trial (n=334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable REVATIO doses (mean dose, 60 mg) for ≥3 months. Patients were randomized to TRACLEER 125 mg twice daily plus REVATIO or placebo plus REVATIO for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (McLaughlin et al, 2015).

TYVASO (treprostinil)

- The safety and efficacy of TYVASO were evaluated in TRIUMPH I, a 12-week, multi-center, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either TRACLEER or REVATIO (n=235) for at least three months prior to study initiation. Patients received either placebo or TYVASO in four daily treatments with a target dose of nine breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and three to five hours after TRACLEER or 30 to 120 minutes after REVATIO. Patients receiving TYVASO had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($P<0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with TYVASO in the pivotal study and the open-label extension (n=206), Kaplan-Meier estimates of survival at one, two, and three years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of TYVASO on mortality.

UPTRAVI (selexipag)

- The safety and efficacy of UPTRAVI were evaluated in the GRIPHON study (n=1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The median duration of treatment varied from 1.2 to 1.4 years for placebo and UPTRAVI, respectively, and treatment end

was defined as seven days after the last day of treatment intake. Compared to placebo, UPTRAVI significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; P<0.001); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of UPTRAVI compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for ~80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with UPTRAVI treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing (P<0.001 for all AEs), anemia (P=0.05), and hyperthyroidism (P=0.004) (Sitbon et al, 2015).

VELETRI (epoprostenol)

- Please refer to the clinical efficacy summary for FLOLAN above.

VENTAVIS (iloprost)

- The efficacy of VENTAVIS was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of VENTAVIS six to nine times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs. 4% placebo, P=0.0033). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this patient population. The placebo-corrected difference in the 6MWD in VENTAVIS patients at 12 weeks was 40 m (P<0.01).
- The safety of VENTAVIS was evaluated in a prospective, two year, open-label study with 63 PAH patients. Patients received VENTAVIS 2 to 4 mcg six to nine times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and eight patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (Olschewski et al, 2010).

Meta-analyses and systematic reviews

- The results of a meta-analysis of 18 randomized controlled trials (n=4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
    - PDE-5 inhibitors were associated with a statically significant reduction in mortality (RR, 0.22; 95% CI, 0.07 to 0.71; P=0.011), while other drugs only showed a trend toward reducing mortality.
    - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, P=0), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (relative risk [RR], 3.41; 95% CI, 2.06 to 5.63; P=0) (Zheng et al, 2014[a]).
- A meta-analysis of 14 randomized controlled trials (n=2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:
    - Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; P=0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; P=0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; P=0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; P=0.837) did not show a benefit.
    - Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; P=0.01), and no heterogeneity (I^2=0.0%; P=0.84) was detected among studies (Zheng et al, 2014[b]).
- The results of a meta-analysis of 21 randomized controlled trials (n=5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
    - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; P=0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; P<0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; P<0.001), and ADEMPAS (OR, 0.277; 95% CI, 0.098 to 0.782; P=0.015).

  - There were no significant reductions in mortality with any class versus placebo (Zhang et al, 2015).
- A meta-analysis of five randomized controlled trials (n=962) of <16 weeks duration in adults and children treated with an sGC stimulator determined the following (all comparisons are vs. placebo):
  - sGC stimulators improve PAP in patients with PAH (who are treatment naïve or receiving a prostanoid or ERA) or those with recurrent or inoperable CTEPH.
  - Pooled analysis showed a mean difference in 6MWD of 30.13 m (95% CI, 5.29 to 54.96; I^2=64%). On subgroup analysis, for PAH, there was no effect on 6MWD (11.91 m; 95% CI, -44.92 to 68.75; I^2=77%), and for CTEPH, sGC stimulators improved 6MWD by a mean difference of 45 m (95% CI, 23.87 to 66.13; I^2=0%).
  - The secondary outcome of mortality showed no change on pooled analysis.
  - Although pooled results demonstrated an increase (improvement) in WHO functional class (OR, 1.53; 95% CI, 0.87 to 2.72; I^2=49%), the results did not reach statistical significance. Also, there was no effect on clinical worsening (OR, 0.45; 95% CI, 0.17 to 1.14; I^2=54%) or a reduction in MAP (−2.77 mmHg; 95% CI, −4.96 to −0.58; I^2=49%). The pooled analysis did not show any significant difference in serious AEs (OR, 1.12; 95% CI, 0.66 to 1.90; I^2=39%).
  - sGC stimulators should not be taken by people also receiving PDE-5 inhibitors or nitrates due to the risks of hypotension, and there is currently no evidence supporting their use in pulmonary hypertension associated with left heart disease (Wardle et al, 2016).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (Ryerson et al, 2010).
  - ERAs (LETAIRIS and TRACLEER) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (REVATIO and ADCIRCA) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (Kuwana et al, 2013).
  - Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (Zhu et al, 2012).
  - Favorable effects on clinical events were not predicted by changes in the 6MWD (Savarese et al, 2012). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (Savarese et al, 2013).
  - According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (McCrory et al, 2013).

Treatment Guidelines

- Several recently published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report on pharmacologic therapy for PAH provides several options for initial and subsequent therapy (Taichman et al, 2014).
    - Initial therapy: For patients in WHO FC II or III, monotherapy with an ERA, PDE-5 inhibitor, or sGC stimulator is recommended. In WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral prostanoid should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (Galiè et al, 2015[b]) provide several options for both monotherapy and combination therapy of PAH.
    - Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be

used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
    - Initial drug combination therapy: Only the combination of ADCIRCA and LETAIRIS has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
    - Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including OPSUMIT added to REVATIO, ADEMPAS added to TRACLEER, and UPTRAVI added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.
  - Reputable society groups agree that evidence supporting pediatric treatment is lacking. The American Heart Association (AHA) and American Thoracic Society (ATS) recently published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (Abman et al, 2015). A recent expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm the AHA/ATS guideline. Additionally, early combination therapy with oral PAH drugs in treatment-naïve children who are FC II or III may be considered (Hansmann et al, 2016).

SAFETY SUMMARY

- sGC Stimulator
  - ADEMPAS has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy (Pregnancy Category X) because it may cause fetal harm when administered to pregnant women.
  - Females can only receive ADEMPAS through the ADEMPAS REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Additional contraindications for ADEMPAS include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).
  - Warnings and precautions for ADEMPAS include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - The most common AEs associated with ADEMPAS include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.
- ERAs
  - The ERAs (LETAIRIS, OPSUMIT, and TRACLEER) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The LETAIRIS and OPSUMIT REMS programs, respectively, are designed in the same manner as the ADEMPAS REMS program described above.
  - The TRACLEER Access Program (T.A.P.) program has been re-listed as the TRACLEER REMS program. As a requirement of the REMS, healthcare professionals who prescribe or dispense TRACLEER must enroll and comply with the requirements. Requirements include monthly reviews of pregnancy tests in women of reproductive potential, and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
  - LETAIRIS has an additional contraindication for idiopathic pulmonary fibrosis.
  - TRACLEER has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for one month after stopping TRACLEER, females of reproductive potential must use two reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Warnings and precautions for ADCIRCA and REVATIO include prolonged erection (for more than four hours), hearing loss, and vision loss (in one or both eyes), all of which require immediate medical attention.

  - Pulmonary edema has been reported during postmarketing surveillance of LETAIRIS and TRACLEER. Pulmonary edema may occur within weeks after starting LETAIRIS and is more common when LETAIRIS is used in combination with ADCIRCA than with LETAIRIS or ADCIRCA alone.
  - Use of OPSUMIT and TRACLEER should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of ADCIRCA and taking nitrates. Additionally, REVATIO and ADCIRCA are contraindicated for concomitant use with the sGC stimulator, ADEMPAS.
  - In August 2012, the prescribing information for REVATIO was updated with a warning stating that the use of REVATIO in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of REVATIO in March 2014, stating it was not intended to suggest that REVATIO never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case REVATIO can be used with close monitoring (FDA Drug Safety Communication, 2014).
  - Co-administration of REVATIO or ADCIRCA with potent CYP3A4 inhibitors is not recommended. Co-administration of ADCIRCA with potent CYP3A4 inducers is not recommended.
  - Blood pressure lowering effects are increased when ADCIRCA is taken with alcohol.
  - REVATIO and ADCIRCA are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.
- Prostacyclin Receptor Agonist
  - UPTRAVI has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - UPTRAVI is not recommended in patients with severe hepatic impairment (Child Pugh Class C) and has not been studied in dialysis patients (or with eGFR <15 mL/min/1.73m^2).
  - UPTRAVI should be avoided when concomitantly administered with strong inhibitors of CYP2C8.
  - The most common AEs reported with UPTRAVI are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - ORENITRAM is contraindicated for use in patients with severe hepatic impairment (Child Pugh Class C).
  - FLOLAN and VELETRI are contraindicated in patients with congestive heart failure due to severe left ventricular dysfunction. Additionally, VELETRI is contraindicated in patients with pulmonary edema
  - ORENITRAM and TYVASO both carry a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Additional warnings and precautions for TYVASO include symptomatic hypotension, possible TYVASO dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in tolerability with hepatic or renal impairment. ORENITRAM should be avoided in patients with blind-end pouches (diverticulosis).
  - The safety of TYVASO and VENTAVIS has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking TYVASO should be carefully monitored to detect any worsening of lung disease and loss of drug effect. VENTAVIS can induce bronchospasm.
  - Hypotension leading to syncope has been observed with VENTAVIS. It should not be administered in patients with a systolic blood pressure below 85 mmHg.
  - With FLOLAN, ORENITRAM, REMODULIN, and VELETRI, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking FLOLAN).
  - FLOLAN carries additional warnings and precautions that include pulmonary edema, vasodilation reactions, and an increased risk of bleeding.
  - Both FLOLAN and REMODULIN are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with FLOLAN. In an open-label study of IV REMODULIN (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about one BSI event per five years of use. A Centers for Disease

Control and Prevention survey of seven sites that used IV REMODULIN for the treatment of PAH found approximately one BSI event per three years of use. Continuous SC infusion (undiluted) is the preferred mode of administration of REMODULIN.

- AEs reported with TYVASO include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with REMODULIN include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with ORENITRAM include headache, diarrhea, nausea, and flushing.
- AEs associated with VENTAVIS include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
- The most common AEs reported with FLOLAN and VELETRI include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ADCIRCA (tadalafil)	Tablet: 20 mg	40 mg once daily	Dividing the dose over the course of the day is not recommended. Use with Ritonavir: In patients receiving ritonavir for at least one week, ADCIRCA should be started at 20 mg once daily. Dose should be increased to 40 mg once daily based on tolerability. During the initiation of ritonavir, ADCIRCA should be avoided. ADCIRCA should be stopped at least 24 hours prior to starting ritonavir. After at least one week, ADCIRCA may be resumed at 20 mg once daily. Dose may be increased to 40 mg once daily based on tolerability.	With or without food
ADEMPAS (riociguat)	Tablet (film-coated): 0.5, 1, 1.5, 2, and 2.5 mg	Initial: 1 mg three times daily Maximum: 2.5 mg three times daily	Starting dose may be lowered to 0.5 mg three times daily in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Dose increases should be no sooner than 2 weeks apart. When switching to ADEMPAS, sildenafil	Patients who smoke may tolerate doses higher than 2.5 mg three times daily. If they stop smoking, dose decreases may be required. For patients who are unable to swallow whole tablets, ADEMPAS may

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			should be discontinued at least 24 hours prior to ADEMPAS administration and tadalafil should be discontinued at least 48 hours prior. ADMEPAS should be discontinued at least 24 hours prior to administering a PDE-5 inhibitor.	be crushed and mixed with water or soft foods.
FLOLAN (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. Abrupt withdrawal or sudden large reductions in infusion rates should be avoided.	Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
LETAIRIS (ambrisentan)	Tablet: 5 and 10 mg	Initial, 5 mg once daily with or without ADCIRCA 20 mg once daily; at four-week intervals, the dose may be increased up to LETAIRIS 10 mg or ADCIRCA 40 mg once daily	Doses >10 mg once daily have not been studied.	With or without food. Tablets should not be split, crushed, or chewed. Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.
OPSUMIT (macitentan)	Tablet: 10 mg	10 mg once daily	Doses >10 mg once daily are not recommended.	-
ORENITRAM (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, and 2.5 mg	Starting dose: 0.25 mg twice daily Maximum dose is determined by tolerability.	Dose should be titrated by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every three to four days as tolerated. Coadministration with CYP2C8 inhibitors (eg,	Should be taken with food Tablets should be swallowed whole When converting from SC/IV to oral routes, use the

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			gemfibrozil) requires a reduced starting dose of 0.125 mg twice daily and can be titrated in 0.125 mg twice daily increments every three to four days.	following equation to estimate the total daily oral dose: ORENITRAM total daily dose (mg) = 0.0072 x SC or IV dose (ng/kg/min) x weight (kg); decrease the SC/IV dose up to 30 ng/kg/min/day while increasing ORENITRAM dose up to 6 mg/day, as tolerated.
REMODULIN (treprostinil)	Multi-dose vials for injection: 20, 50, 100, 200 mg	Continuous infusion should be initiated at a rate of 1.25 ng/kg/min; dose may be reduced to 0.625 ng/kg/min if initial dose cannot be tolerated	The infusion rate should be increased by increments of 1.25 ng/kg/min for the first 4 weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response	SC is preferred, although it can be administered by a central IV line if SC administration is not tolerated
REVATIO (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10 mg/mL Powder for injection: 10 mg	Tablet and powder for oral suspension: 5 or 20 mg three times daily, approximately four to six hours apart Injection: 2.5 mg or 10 mg as an IV bolus 3 times daily	Doses above 20 mg three times daily are not recommended. A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of REVATIO and its metabolite equivalent to that of a 20 mg oral dose.	Should be administered four to six hours apart. The expiration date of the reconstituted oral suspension is 60 days from the date of reconstitution.
TRACLEER (bosentan)	Tablet: 62.5 and 125 mg	Initial: 62.5 mg twice daily for four weeks Maintenance: 125 mg twice daily	Initial and maintenance dose is 62.5 mg twice daily for patients with body weight below 40 kg and over 12 years of age. In patients who have been receiving ritonavir for at least 10 days, TRACLEER should be started at 62.5 mg once daily or every other day based on tolerability. TRACLEER should be discontinued at least 36 hours prior to initiation of ritonavir. After at least 10	Should be administered in the morning and evening, with or without food. Treatment should be initiated in women of reproductive potential only after a negative pregnancy test. Monthly pregnancy tests should be conducted during treatment.

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			days following the initiation of ritonavir, TRACLEER should be resumed at 62.5 mg once daily or every other day based on tolerability.	
TYVASO (treprostinil)	Inhalation solution: 0.6 mg/mL (1.74 mg per 2.9 mL)	Initial: Three breaths (18 mcg), per treatment session, four times a day (four hours apart) during waking hours. Maximum: Nine breaths per treatment session, four times daily.	If three breaths are not tolerated, the number of breaths may be reduced to one to two and subsequently increased to three breaths as tolerated. Dosage should be increased by an additional three breaths at approximately one to two week intervals, if tolerated, until the target dose of nine breaths (54 mcg) is reached per treatment session, four times daily.	The inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.
UPTRAVI (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg	Initial: 200 mcg orally twice daily. Dose should be titrated weekly in increments of 200 mcg twice daily. Maximum: 1600 mcg twice daily	If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.	If treatment is missed for ≥ three days, UPTRAVI should be started at a lower dose and retitrated.
VELETRI (epoprostenol)	Powder for injection: 0.5, 1.5 mg	Initial: 2 ng/kg/min continuous infusion; dose may be increased in increments of 1 to 2 ng/kg/min every 15 minutes based on clinical response.	If dose-limiting pharmacologic effects occur, the infusion rate should be decreased gradually until tolerated. Abrupt withdrawal or sudden large reductions in infusion rates should be avoided.	Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
VENTAVIS (Iloprost)	Inhalation solution: 10, 20 mcg	Initial: 2.5 mcg via inhalation. Maintenance: 2.5 to 5 mcg, based on tolerability. VENTAVIS is administered six to nine times per day (no more than once every two hours)	Vital signs should be monitored while initiating VENTAVIS	VENTAVIS is intended to be inhaled using the I-neb Adaptive Aerosol Delivery (AAD) System The 20 mcg/mL concentration is for patients who are maintained at

DRUG	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		during waking hours, according to individual need and tolerability.		the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing.

Abbrv: CYP = cytochrome P450; IV = intravenous; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ADCIRCA (tadalafil)	No dose adjustment is required in patients >65 years of age without renal or hepatic impairment. A greater sensitivity in some older patients should be considered.	Safety and efficacy have not been established.	Mild (CrCL 51 to 80 mL/min) or moderate (CrCL 31 to 50 mL/min): Start dose at 20 mg once daily. Increase to 40 mg daily based on individual tolerability. Severe (CrCL<30 mL/min and on hemodialysis): Avoid use**	Mild or moderate (Child Pugh Class A or B): Consider starting dose of 20 mg once per day due to limited clinical experience. Severe (Child Pugh Class C): Not studied, avoid use.	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
ADEMPAS (riociguat)	No dose adjustments required in older patients (65 years and older). A greater sensitivity in some older patients cannot be ruled out.	Safety and efficacy have not been established.	Not recommended in patients with CrCL <15 mL/min or on dialysis	Not recommended in patients with severe liver impairment (Child Pugh C)	Pregnancy category X Discontinue nursing or the drug.
FLOLAN (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
LETAIRIS (ambrisentan)	The elderly (age ≥65years) showed less improvement in walk distances than younger patients. However no specific dose adjustments are needed.	Safety and efficacy have not been established.	Dose adjustment in patients with mild or moderate renal impairment is not required. There is no information for patients with severe renal impairment.	Not recommended in patients with moderate or severe hepatic impairment. Discontinue LETAIRIS if elevations of liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.	Pregnancy category X Discontinue nursing or the drug.
OPSUMIT (macitentan)	No dose adjustments required in patients ≥65 years.	Safety and efficacy have not been established.	Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15 to 29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.	Exposure to OPSUMIT was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.	Pregnancy category X Discontinue nursing or the drug.
ORENITRAM (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	No dose adjustments are required.	Mild (Child Pugh Class A): Initial, 0.125 mg twice daily. Titrate by 0.125 mg every three to four days Moderate (Child Pugh Class B): Avoid use Severe (Child Pugh Class C): Contraindicated	Pregnancy category C Discontinue nursing or the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
REMODULIN (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Clinical studies did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.	Not studied	Mild to moderate: Initial dose should be decreased to 0.625 ng/kg/min ideal body weight, and monitored closely Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
REVATIO (sildenafil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Use of REVATIO, particularly chronic use, is not recom-mended in children.	No dosage adjustment required (including with severe impairment CrCL <30 mL/min)	Mild to moderate: No dose adjustment Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.
TRACLEER (bosentan)	Clinical studies of TRACLEER did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.	Safety and efficacy have not been established.	No dosing adjustments required	Moderate to Severe (Child Pugh Class B and C): Avoid use.	Pregnancy category X Discontinue nursing or the drug.
TYVASO (treprostinil)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients.	Safety and efficacy have not been established.	Not studied	Mild to moderate: Slow up-titration is recommended. Severe: Not studied	Pregnancy category B Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
UPTRAVI (selexipag)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	No dosing adjustments required in patients with eGFR >15 mL/min/1.73 m^2. Not studied in dialysis patients or in eGFR <15 mL/min/1.73 m^2.	Mild (Child Pugh Class A): No dose adjustment necessary Moderate (Child Pugh Class B): Starting dose of 200 mcg once daily; titrate weekly by 200 mcg once daily Severe (Child Pugh Class C): Not studied, avoid use.	No human studies; animal models show no clinically relevant effects on embryofetal development. Discontinue drug or breastfeeding.
VENTAVIS (iloprost)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category C Discontinue nursing, due to the importance of the drug to the mother.
VELETRI (epoprostenol)	Clinical studies did not include a sufficient number of patients ≥65 years of age to determine if they respond differently from younger patients. Dose selection should be cautious.	Safety and efficacy have not been established.	Not studied	Not studied	Pregnancy category B Unknown; use with caution.

Abbrv: CrCL = creatinine clearance; eGFR=estimated glomerular filtration rate; ULN = upper limit of normal
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an AE on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from AE data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
**Due to increased ADCIRCA exposure (AUC), limited clinical experience, and lack of ability to influence clearance by dialysis

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.

- There are five classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (LeVarge et al, 2015). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (Galiè et al, 2015[a]; McLaughlin et al, 2015; Pulido et al, 2013; Sitbon et al, 2015).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data is conflicting regarding the benefits of combination vs. monotherapy (Barst, 2009; McLaughlin et al, 2009; Galiè et al, 2015[b]; Taichman et al, 2014). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with LETAIRIS and ADCIRCA resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (Galiè et al, 2015[a]). However, the COMPASS-2 trial demonstrated no difference between TRACLEER plus REVATIO versus REVATIO monotherapy for most endpoints with the exception of the mean 6MWD test (McLaughlin et al, 2015).
- ADEMPAS is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. ADEMPAS is dosed three times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (LETAIRIS, OPSUMIT, and TRACLEER) competitively bind to both receptors with different affinities. LETAIRIS and OPSUMIT are highly selective for the ET_A receptor, while TRACLEER is slightly selective for the ET_A receptor over the ET_B receptor. In addition, OPSUMIT has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (ADCIRCA and REVATIO) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of ADCIRCA with potent CYP3A4 inhibitors or inducers may significantly alter serum levels of ADCIRCA and is not recommended. Use of ADCIRCA in patients who are using an sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is not recommended. Use of REVATIO with potent CYP3A4 inhibitors is not recommended as they may significantly alter serum levels of REVATIO.
- In addition to the oral formulation, REVATIO is available in an oral suspension formulation and an intravenous formulation. Currently, REVATIO tablets and intravenous formulation are available generically.
- ADCIRCA is taken just once a day compared to three times a day with REVATIO.
- ORENITRAM is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, ORENITRAM may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. ORENITRAM is dosed twice daily and requires dosage titration every 3 to 4 days. ORENITRAM did not demonstrate added benefit when added to other vasodilator therapy.
- UPTRAVI is a first-in-class prostacyclin receptor agonist, which works within the same pathway as ORENITRAM. Based on results from the GRIPHON trial, UPTRAVI has reduced disease progression and hospitalization. This is in contrast to ORENITRAM, which has only improved exercise tolerability. Unlike ORENITRAM, UPTRAVI has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of UPTRAVI compared to other oral agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by ~80% of patients within the placebo baseline group. Those AEs reported significantly more often with UPTRAVI treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (Sitbon et al, 2015). Based on indirect trial evidence, the proportion of patients discontinuing UPTRAVI vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the ORENITRAM labeling vs. placebo (4% vs. 3%) (ORENITRAM prescribing information, 2014; Sitbon et al, 2015). Overall, it is not clear how the UPTRAVI safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.

- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (Taichman et al, 2014).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines stratifies PAH treatment by low or intermediate risk or high risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs are recommended with epoprostenol IV considered first-line due to the mortality benefits in trials (Galiè et al, 2015[b]).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (Abman et al, 2015; Galiè et al, 2015[b]; Hansmann et al, 2016). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (Abman et al, 2015). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines taking in account risks (Galiè et al, 2015[b]). The European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with two oral PAH drugs in treatment-naïve children who are FC II or III may be considered (Hansmann et al, 2016).

Table 5. Advantages and Disadvantages of PAH Agents

Drug	Advantages	Disadvantages
ERAs		
LETAIRIS (ambrisentan)	• Highly selective potent ET_A receptor antagonist • Indicated for treatment of PAH in patients with WHO Class II or III symptoms, to improve exercise capacity and to delay clinical worsening • Administered once daily with or without food (may require titration)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Contraindication in patients with IPF, including IPF patients with pulmonary hypertension (WHO Group III) • Not recommended for use in patients with moderate or severe hepatic impairment
OPSUMIT (macitentan)	• Newest ERA indicated to delay disease progression • "Tissue-targeting" in human pulmonary arterial smooth muscle cells • Administered once daily with or without food (no titration required)	• Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program • Requires baseline and periodic lab tests prior to treatment initiation

Drug	Advantages	Disadvantages
TRACLEER (bosentan)	• First oral agent to be approved for PAH • Efficacy demonstrated as both monotherapy and in combination treatment	• Administered twice daily • Non-selectively blocks both ET_A and ET_B receptors • Boxed warning for teratogenicity with required participation in REMS restricted distribution program • Additional boxed warning related to hepatotoxicity • Use in patients with moderate to severe hepatic impairment should be avoided • Contraindication in patients receiving either cyclosporine A or glyburide • Potential teratogenic effects • Multiple drug interactions
PDE-5 inhibitors		
ADCIRCA (tadalafil)	• Administered once daily with or without food • Efficacy demonstrated as both monotherapy and in combination treatment	• Contraindicated with concomitant organic nitrates and sGC stimulator • Dose reductions needed in patients with mild and moderate renal and hepatic impairment
REVATIO (sildenafil)	• Available in multiple formulations (tablets, injection, and oral suspension) • Generic availability	• Administered three times daily • Contraindicated with concomitant organic nitrates and sGC stimulator
Prostacyclin receptor agonist		
UPTRAVI (selexipag)	• First in class, prostacyclin receptor agonist • Efficacy demonstrated as both monotherapy and in combination treatment (with an ERA and/or PDE-5 inhibitor)	• Administered twice daily • Requires dose titration between 200 mcg and 1600 mcg twice daily • Requires dose reduction in moderate hepatic impairment; not recommended for use in severe hepatic impairment
PCAs		
FLOLAN (epoprostenol)	• First approved drug for the treatment of PAH, so more data and experience with this drug • Generic availability	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose decreases • Vials must be refrigerated and infusion must be kept cool with ice packs (unless reconstituted solution was prepared with pH 12 sterile diluent for FLOLAN, in which case it is stable for 72 hours at a room temperature of up to 77°F)
ORENITRAM (treprostinil)	• First FDA-approved oral PCA	• Administered twice daily • Contraindicated in patients with Child-Pugh Class C hepatic impairment • Tablets must be swallowed whole and taken with food • Has not demonstrated benefit in combination therapy. • Abruptly lowering the dose or withdrawing the drug should be avoided

Drug	Advantages	Disadvantages
REMODULIN (treprostinil)	• Can be administered SC as an alternative to IV administration • Longer half-life compared to FLOLAN • Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used	• Risk of BSI due to use of an indwelling central venous catheter with IV administration • Pain associated with SC administration
TYVASO (treprostinil)	• Administered via inhalation	• Must be administered 4 times daily, at equally spaced intervals • Safety and efficacy of have not been established in patients with significant underlying lung disease (eg, asthma or chronic obstructive pulmonary disease)
VELETRI (epoprostenol)	• Vials and solution are stable at room temperature (no need for ice packs), regardless of which compatible diluent is used • Reconstitution easier and more flexible	• Risk of BSI due to use of an indwelling central venous catheter • Requires use of complex delivery system • Risk of rebound PH with abrupt discontinuation or large dose reductions
VENTAVIS (iloprost)	• Administered via inhalation	• Frequent administration is required (6 to 9 times daily). • May cause bronchospasm, especially in patients with a history of hyperreactive airway disease
sGC stimulator		
ADEMPAS (riociguat)	• First in class, sGC stimulator • First FDA-approved treatment for CTEPH (WHO Group IV) • Tablets can be crushed and mixed with water or soft foods for those patients who are unable to swallow tablets whole	• Administered three times daily • Requires lower initial doses in patients with intolerable hypotensive effects • Requires higher doses in patients who smoke • Boxed warning for embryo-fetal toxicity and required REMS restricted distribution program

REFERENCES

- Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015 Nov 24;132(21):2037-99.
- ADCIRCA prescribing information. Eli Lilly and Company. Indianapolis, IN. May 2017.
- ADEMPAS prescribing information. Bayer Healthcare Pharmaceuticals. Whippany, NJ. February 2017.
- Archer, SL. Riociguat for pulmonary hypertension – a glass half full. *N Engl J Med*. 2013;369(4):386-88.
- Asaki T, Kuwano K, Morrison K, et al. Selexipag: An oral and selective IP prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *J Med Chem*. 2015 Sep 24;58(18):7128-37.
- Badesch DB, Feldman J, Keogh A, et al. ARIES-3: Ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc Ther.* 2012 Apr;30(2):93-9.
- Barst RJ, Gibbs US, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54:S78.
- Buckley MS, Staib RL, Wicks LM. Combination therapy in the management of pulmonary arterial hypertension. Int J Clin Pract Suppl. 2013;(179):13-23.
- Channick RN, Delcroix M, Ghofrani HA, et al. Effect of macitentan on hospitalizations: results from the SERAPHIN trial. *J Am Coll Cardiol HF*. 2015;3:1-8.
- Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. *Lancet*. 2001 Oct 6;358(9288):1119-23.
- DRUGS@FDA.com: Approved drug products with therapeutic equivalence evaluations. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/ . Accessed June 30, 2017.
- Facts & Comparisons. Facts & Comparisons website. www.factsandcomparisons.com.. Accessed July 1, 2017.
- Flolan prescribing information. GlaxoSmithKline. Research Triangle Park, NC. June 2016.

- Food and Drug Administration (FDA) Drug Safety Communication: FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension. August 30, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm. Accessed June 30, 2017.
- Food and Drug Administration (FDA) Drug Safety Communication: FDA clarifies warning about pediatric use of Revatio (sildenafil) for pulmonary arterial hypertension. March 31, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm390876.htm. Accessed June 30, 2017.
- Galiè N, Barberà JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION). *N Engl J Med.* 2015 Aug 27 [a];373(9):834-44.
- Galiè N, Brundage BH, Ghofrani HA, et al. Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009 Jun 9;119(22):2894-903.
- Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005 Nov 17;353(20):2148-57.
- Galiè N, Humbert M, Vachiery JL, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), International Society of Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015 Oct [b];46(4):903-75.
- Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008 Jun 10[a];117(23):3010-9.
- Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008 Jun 21[b];371(9630):2093-100.
- Ghofrani HA, D'Armini AM, et al. Riociguat for the treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med*. 2013[a];369:319-29.
- Ghofrani HA, Galiè N, et al. Riociguat for the treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2013[b];369:330-40.
- Ghofrani HA, Grimminger F, Grunig E, et al. Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomized, long-term extension trial. *Lancet Respir Med*. 2016;4:361-71.
- Gomberg-Maitland M, Dufton C, Oudiz RJ, Benza RL. Compelling evidence of long-term outcomes in pulmonary arterial hypertension? A clinical perspective. J Am Coll Cardiol. 2011;57(9):1053-61.
- Hansmann G, Apitz C; for the European Paediatric Pulmonary Vascular Disease Network. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. Endorsed by the International Society of Heart and Lung Transplantation (ISHLT) and the German Society of Paediatric Cardiology (DGPK). *Heart*. 2016;102:ii67-85.
- Jing XC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized controlled trial (FREEDOM-M). *Circulation*. 2013;127:624-33.
- Kuwana M, Watanabe H, Matsuoka N, Sugiyama N. Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials. *BMJ Open*. 2013;3(8):e003113.
- LETAIRIS prescribing information. Gilead Sciences. Foster City, CA. October 2015.
- LeVarge BL, Channick RN. The changing paradigm in pulmonary hypertension trials: longer duration, new endpoints. *Curr Opin Pulm Med.* 2015;21:438-445.
- McCrory DC, Coeytaux RR, Schmit KM, et al. Pulmonary arterial hypertension: screening, management, and treatment. Comparative Effectiveness Review No. 117. Rockville, MD: Agency for Healthcare Research and Quality. 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
- McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009 Apr 28;119(16):2250-94.
- McLaughlin VV, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension (COMPASS-2). *Eur Respir J.* 2015 Aug;46(2):405-13.
- McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. A*m J Respir Crit Care Med*. 2006 Dec 1;174(11):1257-63.
- Olschewski H, Hoeper M, Behr J, et al. Long-term therapy with inhaled iloprost in patients with pulmonary hypertension. *Respir Med*. 2010;104(5):731-40.
- OPSUMIT prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. March 2017.
- ORENITRAM prescribing information. United Therapeutics. Research Triangle Park, NC. January 2017.
- Oudiz RJ, Brundage BH, Galiè N, et al. Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study. *J Am Coll Cardiol.* 2012 Aug 21;60(8):768-74.
- Oudiz RJ, Galiè N, Olschewski H, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009 Nov 17;54(21):1971-81.
- Pogue KT, Walter CP. Pulmonary Arterial Hypertension. In: Murphy JE, Lee MW, eds. Pharmacotherapy Self-Assessment Program, 2016 Book 1. Cardiology. Lenexa, KS: American College of Clinical Pharmacy, 2016:61-81.
- Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-18.
- REMODULIN prescribing information. United Therapeutics Corporation. Research Triangle Park, NC. December 2014.
- REVATIO prescribing information. Pfizer. NY, NY. April 2015.
- Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002 Mar 21;346(12):896-903.
- Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. *Chest*. 2011 Nov;140(5):1274-83.
- Rubin LJ, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). *Eur Respir J*. 2015;45:1303-13.
- Rubin LJ, Hopkins W. Clinical features and diagnosis of pulmonary hypertension in adults. UpToDate Web site. 2017. www.uptodate.com. Accessed June 30, 2017.

- Ryerson CJ, Nayar S, Swiston JR, Sin DD. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res*. 2010;11:12.
- Savarese G, Musella F, D'Amore C, et al. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. *Eur Respir J*. 2013;42(2):414-24.
- Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol*. 2012;60(13):1192-201.
- Simonneau G, D'Armini AM, Ghofrani H, et al. Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomized, long-term extension trial. *Lancet Respir Med*. 2016; 4:372-80.
- Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-41.
- Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009 Jun 30;54(1 Suppl):S43-54.
- Simonneau G, Rubin LJ, Galiè N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008 Oct 21;149(8):521-30.
- Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension (GRIPHON). *N Engl J Med.* 2015 Dec 24;373(26):2522-33.
- Stringham R, Shah NR. Pulmonary arterial hypertension: an update on diagnosis and treatment. *Am Fam Physician*. 2010;82(4):370-377.
- Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST Guideline and Expert Panel Report. *Chest*. 2014;146(2):449-75.
- Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C Study). *Chest*. 2012; 142(6):1383-90.
- Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C2 Study). *Chest*. 2013; 144(3):952-8.
- TRACLEER prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. October 2016.
- TYVASO prescribing information. United Therapeutics Corporation. Research Triangle Park, NC. June 2016.
- UPTRAVI prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. December 2015.
- VELETRI prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. July 2016.
- VENTAVIS prescribing information. Actelion Pharmaceuticals. South San Francisco, CA. November 2013.
- Wardle AJ, Seager MJ, Wardle R, et al. Guanylate cyclase stimulators for pulmonary hypertension. Cochrane Database Syst Rev. 2016;8:1-43.
- Waxman AB. Oral prostacyclin therapy for pulmonary arterial hypertension: another step forward. *Circulation*. 2013;127:563-5.
- Wu Y, O'Callaghan DS, Humbert M. An update on medical therapy for pulmonary arterial hypertension. Curr Hypertens Rep. 2013;15(6):614-22.
- Zhang HD, Zhang R, Jiang X, et al. Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: a systematic review and meta-analysis. *Am Heart J.* 2015;170:96-103.e14.
- Zheng YG, Ma H, Hu EC, et al. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. *Pulm Pharmacol Therap*. 2014 [a];29:241-49.
- Zheng Y, Yang T, Chen G, et al. Prostanoid therapy for pulmonary arterial hypertension: a meta-analysis of survival outcomes. *Eur J Clin Pharmacol.* 2014 [b];70(1):13-21.
- Zhu B, Wang L, Sun L, Cao R. Combination therapy improves exercise capacity and reduces risk of clinical worsening in patients with pulmonary arterial hypertension: a meta-analysis. *J Cardiovasc Pharmacol.* 2012;60(4):342-6.

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Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (Longstreth, 2017).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (Hesketh, 2017[a], National Cancer Institute, 2017).
- The precise mechanism by which chemotherapy induces n/v remains unclear; however, it is known to involve several areas in the central and peripheral nervous systems and the GI tract. Some chemotherapy agents may interact with receptors in areas of the brainstem, leading to activation of the vomiting center. In addition, chemotherapy may cause intestinal cell damage and the release of serotonin (5-hydroxytryptamine [5-HT]), with subsequent activation of emetic reflexes. More than 30 neurotransmitters have been associated with nervous system sites involved in CINV; the most clinically relevant of these are dopamine, 5-HT, and substance P (Hesketh et al, 2016).
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (Longstreth, 2017).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (Feyer et al, 2017).
- Nausea with or without vomiting is common in early pregnancy and affects 70 to 85% of pregnant women. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (American College of Obstetrics and Gynecologists [ACOG] 2015, Smith et al, 2017).
- The mechanism of action for the 5-HT_3 agents results from the blockade of 5-HT_3 receptors in both the gastric area and the chemoreceptor trigger zone in the central nervous system (CNS). By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (Mannix et al, 2006).
- The substance P/neurokinin 1 (NK_1) receptor antagonists cross the blood brain barrier and occupy the NK_1 receptors in the brain, leading to reduced symptoms of n/v.
- The mechanism of action of DICLEGIS® and BONJESTA® (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown; however, doxylamine is known to compete with histamine for H1-receptor sites and block the chemoreceptor trigger zone thereby decreasing n/v (Smith et al, 2017).
- The 5-HT_3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The substance P/NK_1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, AKNYZEO®, contains palonosetron, a 5-HT_3 receptor antagonist, and netupitant, a substance P/NK_1 receptor antagonist. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- DICLEGIS and BONJESTA are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. DICLEGIS and BONJESTA are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
- The combination of doxylamine and pyridoxine was previously available in the United States under the brand name BENDECTIN®. However this product was removed from the market in 1983 due to law suits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis of controlled studies on outcome of pregnancies exposed to Bendectin® reported no increase in the incidence of birth defects (Smith et al, 2017).

- Medispan Therapeutic Class: 5-HT_3 Receptor Antagonists; Substance P/NK_1 Receptor Antagonists; Antiemetic Combinations – Two Ingredient; Miscellaneous.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALOXI® (palonosetron) IV injection*	Eisai, Inc.	07/25/2003	-†
ANZEMET® (dolasetron) injection	Sanofi-Aventis U.S.	09/11/1997	-
ANZEMET (dolasetron) tablets	Sanofi-Aventis U.S.	09/11/1997	-
BONJESTA (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	Duchesnay, Inc.	11/07/2016	-
DICLEGIS (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	Duchesnay, Inc.	04/08/2013	-
granisetron injection	Various	12/29/1993 (KYTRIL®)	√‡
granisetron tablets	Various	03/16/1995 (KYTRIL)	√‡
SANCUSO® (granisetron) transdermal patch	Prostrakan, Inc.	09/12/2008	-
SUSTOL® (granisetron) extended-release injection	Heron Therapeutics	08/09/2016	-
ZOFRAN® (ondansetron) injection	GlaxoSmithKline	01/04/1991	√‡
ZOFRAN (ondansetron) tablet	GlaxoSmithKline	12/31/1992	√‡
ZOFRAN ODT® (ondansetron) orally disintegrating tablet	GlaxoSmithKline	01/27/1999	√‡
ZOFRAN (ondansetron) oral solution	GlaxoSmithKline	01/24/1997	√‡
ZUPLENZ® (ondansetron) oral soluble film	Galena Biopharma, Inc.	07/02/2010	-
EMEND® (aprepitant) capsule	Merck & Co., Inc.	03/26/2003	√
EMEND (aprepitant) oral suspension	Merck & Co., Inc.	12/17/2015	-
EMEND (fosaprepitant) injection	Merck & Co., Inc.	10/12/2010	-**
VARUBI™ (rolapitant) tablet	Tesaro, Inc.	09/01/2015	-
AKYNZEO (palonosetron/netupitant) capsule	Eisai, Inc.	10/10/2014	-

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
*FDA approved ALOXI as an oral capsule on August 22, 2008, but neither Helsinn Healthcare nor Eisai have ever marketed ALOXI capsules. ALOXI oral capsules are listed on FDA's web site as "discontinued."
**Sandoz received FDA approval for generic EMEND injection on September 24, 2012. However, patents will likely protect EMEND injection from generic competition until March 4, 2019, pending patent litigation.
†Generics listed in the FDA Orange Book but are not yet marketed.
‡Generic available in at least one dosage form and/or strength.

(DRUGS@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. FDA-Approved Indication

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Highly emetogenic cancer chemotherapy – prevention of acute n/v associated with initial and repeat courses in adults				√					
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy								√	
Moderately emetogenic cancer chemotherapy – prevention of acute and delayed n/v associated with initial and repeat courses in adults				√					
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy in patients ≥6 months of age					√ (oral suspension)				
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including				√					

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
highly emetogenic chemo in pediatric patients aged one month to <17 years									
Prevention of acute and delayed n/v associated with initial and repeat courses of highly emetogenic cancer chemo-therapy, including high-dose cisplatin, when used in combination with other antiemetic agents						√	√		
Prevention of acute and delayed n/v associated with initial and repeat courses of highly emetogenic cancer chemo-therapy, including high-dose cisplatin, when used in combination with other antiemetic agents in patients ≥12 years of age					√ (capsule)				
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy when used in combination with other antiemetic agents							√		
Prevention of n/v associated with initial and repeat courses of						√			

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
moderately emetogenic cancer chemotherapy when used in combination with other antiemetic agents									
Prevention of n/v associated with initial and repeat courses of moderately emetogenic cancer chemotherapy when used in combination with other antiemetic agents in patients ≥12 years of age					√ (capsule)				
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated				√					

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
Prevention of postoperative nausea and/or vomiting; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur postoperatively; in patients in whom nausea and/or vomiting must be avoided postoperatively, ZOFRAN injection is recommended even when the incidence of PONV is low; for patients who do not receive prophylactic ZOFRAN injection and experience n/v postoperatively, ZOFRAN injection may be given to prevent further episodes			√ (injection)						
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥6 months of age			√ (injection)						
Prevention of n/v associated with initial and repeat courses of moderately emetogenic cancer chemotherapy			√ (tablet, ODT, oral solution, oral soluble film)		√ (oral suspension)				
Prevention of n/v associated with highly			√ (tablet, ODT,						

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
emetogenic cancer chemotherapy including cisplatin ≥ 50 mg/m^2			oral solution, oral soluble film)						
Prevention of PONV in adults					√ (capsule)				
Prevention of PONV in adults and children two years and older; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, ANZEMET injection is recommended even where the incidence of PONV is low. Do not rechallenge a patient who has failed a previous trial of a 5-HT_3 receptor antagonist with a repeat dose of dolasetron.	√ (injection)								
Prevention of n/v in patients receiving moderately and/or highly emetogenic chemotherapy for up to five consecutive days		√ (transdermal patch)							
Prevention of n/v associated with moderately emetogenic cancer chemotherapy, including	√ (tablet)								

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
initial and repeat courses in adults and children two years and older									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		√ (injection, tablets)							
Prevention of n/v associated with radiation, including TBI and fractionated abdominal radiation		√ (tablets)							
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose fraction to the abdomen, or daily fractions to the abdomen			√ (tablet, ODT, oral solution, oral soluble film)						
Treatment of n/v of pregnancy in women who do not respond to conservative management									√
Treatment of postoperative nausea and/or vomiting in adults and children two years and older	√ (injection)								
Prevention of postoperative nausea and/or vomiting; as with other antiemetics, routine prophylaxis is not		√ (injection)	√ (tablet, ODT, oral solution, oral soluble film)						

Indication	5-HT_3 Receptor Antagonists				Substance P/NK_1 Receptor Antagonists			Combination Product	Miscellaneous
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Palonosetron/ netupitant	Doxylamine succinate/ pyridoxine HCl
recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.									
Prevention of acute and delayed n/v associated with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens, in combination with other antiemetics.		√ (extended-release injection)							

Abbrv: ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, TBI=total body irradiation

(Prescribing information: AKYNZEO, 2015; ALOXI, 2015; ANZEMET injection, 2014; ANZEMET tablets, 2014; BONJESTA, 2016; DICLEGIS tablets, 2013; EMEND capsules and oral suspension, 2017; EMEND for injection, 2016; granisetron injection, 2015; granisetron tablets, 2015; ondansetron, 2014; SANCUSO, 2015; SUSTOL, 2016; VARUBI 2015; ZOFRAN injection, 2014; ZOFRAN, tablets, ODT, oral solution, 2016; ZUPLENZ, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

CINV

- ANZEMET (dolasetron) has been shown to be an effective therapy in the treatment of CINV in comparative studies with ALOXI (palonosetron), ZOFRAN (ondansetron), and placebo (Eberhart et al, 2004; Eisenberg et al, 2003; Karamanlioglu et al, 2003; Lofters et al, 1997; Meyer et al, 2005, Walker et al, 2001).
- Granisetron and ZOFRAN (ondansetron) are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of one over another, but this has not been a consistently proven outcome (Billio et al, 2010; Dabbous et al, 2010; del Giglio et al, 2000; Dempsey et al, 2004; Gan et al, 2005; Jaing et al, 2004; Kalaycio et al, 1998; Lacerda et al, 2000; Orchard et al, 1999; White et al, 2006).
- Granisetron and ZOFRAN (ondansetron) have also been shown to be effective in the treatment of RINV (Spitzer et al, 2000; Salvo et al, 2012).
- SANCUSO (granisetron) patch was non-inferior to orally administered granisetron for CINV (Boccia et al, 2011).
- ALOXI (palonosetron) was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (Aapro et al, 2005; Billio et al, 2010; Botrel et al, 2011; Dong et al, 2011; Eisenberg et al, 2003; Gralla et al, 2003; Kaushal et al, 2010; Likun et al, 2011; Massa et al, 2009; Suzuki et al, 2016).
- The safety and efficacy of SUSTOL (granisetron ER) were evaluated in a pivotal Phase 3 double-blind, double-dummy, multicenter, randomized controlled trial in adults receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy (Raftopoulos et al, 2015[a], Raftopoulos et al, 2015[b]). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after highly and moderately emetogenic chemotherapy. The FDA-approved dose of granisetron ER 10 mg was non-inferior to palonosetron in preventing delayed CINV after moderately emetogenic chemotherapy and was not superior in preventing delayed CINV after highly emetogenic chemotherapy (Raftopoulos et al, 2015[a], Raftopoulos et al, 2015[b]).
- All of the 5-HT_3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate meta-analyses and are superior to placebo (Billio et al, 2010; del Giglio et al, 2000; George et al, 2009; Singhal et al, 2012; Tang et al, 2012). A 2016 meta-analysis comparing ondansetron to other 5-HT_3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (Simino et al, 2016).
- A 2016 Cochrane review found that 5-HT_3 receptor antagonists are effective in children who receive emetogenic chemotherapy (Phillips et al, 2016). Granisetron or ALOXI (palonosetron) may be more effective than ZOFRAN (ondansetron), and the addition of dexamethasone improves vomiting symptoms.
- A randomized, double-blind, non-inferiority study comparing single-dose palonosetron (20 mcg/kg) to multi-dose ondansetron (150 mcg/kg x 3 doses) for the prevention of CINV in pediatric patients (0 to 17 years) receiving moderately or highly emetogenic chemotherapy found that palonosetron was non-inferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (Kovacs et al, 2016).
- A randomized, double-blind study in patients receiving highly emetogenic chemotherapy found that when used as part of combination therapy with dexamethasone and EMEND (aprepitant), intravenous palonosetron was not more efficacious than intravenous granisetron at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (Suzuki et al, 2016).
- One multicenter, double-blind, randomized controlled trial evaluated dexamethasone compared to EMEND (aprepitant) in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (i.e., no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and EMEND (aprepitant) in the prevention of delayed emesis (Roila et al, 2014).
- EMEND (aprepitant) has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT_3 antagonists and/or dexamethasone (Herrington et al, 2008; Rapoport et al, 2010; Yeo et al, 2009; Herrstedt et al, 2005; Warr et al, 2005; Gralla et al, 2005; De Wit et al, 2004; Poli-Bigelli et al, 2003; Hesketh et al, 2003; Martin et al, 2003; Gore et al, 2009; Jordan et al, 2009; Grunberg et al, 2009).
- In combination regimens with granisetron and dexamethasone, VARUBI (rolapitant) has been shown to be more effective than placebo for the prevention of CINV due to moderately and highly emetogenic chemotherapy in clinical trials (Rapoport et al, 2015; Schwartzberg et al, 2015). In combinations with 5-HT_3 antagonists and dexamethasone, addition of VARUBI (rolapitant) has also been shown to be more effective at preventing CINV

over multiple cycles of moderately or highly emetogenic chemotherapy, when compared to similar combinations without rolapitant (Rapoport et al, 2016).
- The fixed-dose combination AKYNZEO (palonosetron and netupitant) + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following moderately emetogenic chemotherapy (Aapro et al, 2014); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (Gralla et al, 2014).

PONV

- In a meta-analysis, ALOXI (palonosetron) was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ZOFRAN (ondansetron) (Xiong et al, 2015).
- A 2016 meta-analysis found that when compared to other 5-HT3 antagonists and NK_1 antagonists, EMEND (aprepitant) reduces incidence of PONV, and need for rescue medications (Singh et al, 2016).

Pregnancy
- FDA-approvals of DICLEGIS and BONJESTA were based on one double-blind, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with nausea and vomiting. Patients (N=298) were randomized to 14 days of placebo or two tablets daily at bedtime and up to a maximum dose of four tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (P=0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the DICLEGIS group compared to a 1.8 point decrease in the placebo group (P=0.005) (Koren et al, 2010).
    - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (Koren et al, 2015).

Guidelines
- The 5-HT_3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV (American Gastroentrological Association [AGA], 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Gan et al, 2014; Gupta et al, 2016; Roila et al, 2010).
- Treatment of CINV or RINV generally involves the use of multiple agents that affect different receptor types (AGA, 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Roila et al, 2010).
    - The 2016 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (Hesketh et al, 2016):
        - For the prevention of n/v induced by highly emetogenic chemotherapy agents, a three drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone is recommended as first-line therapy.
        - For moderately emetogenic agents, a two-drug combination of ALOXI (palonosetron) and dexamethasone is recommended.
        - For children receiving highly or moderately emetogenic agents, a 5-HT_3 receptor antagonist plus a corticosteroid is recommended.
    - The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (Gupta et al, 2016):
        - All patients should receive PONV prophylaxis during the perioperative period.
        - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
    - The 2015 ACOG Practice Bulletin for nausea and vomiting of pregnancy recommends the following:
        - Mild cases of nausea and vomiting may be resolved with lifestyle and dietary changes such as eating frequent small meals or avoiding spicy or fatty foods.
        - First-line pharmacotherapy with pyridoxine or in combination with doxylamine.

- If initial therapy with pyridoxine monotherapy is inadequate, then the addition of doxylamine is recommended.

SAFETY SUMMARY

- The Antiemetics – 5-HT_3 Receptor Antagonists and Substance P/NK_1 Receptor Antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAIO), as they intensify and prolong the adverse effects of the agent.
- EMEND is contraindicated in patients taking pimozide due to the risk of significantly increased plasma concentrations of pimozide, potentially resulting in prolongation of the QT interval. VARUBI is contraindicated in patients taking thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Pointes.
- The 5-HT_3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for ANZEMET (dolasetron) regarding the risk of arrhythmias. ZOFRAN (ondansetron) and granisetron have QTc prolongation as a general precaution, but the incidence of electrocardiogram (ECG) changes has been less than 1%. In addition, the development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists.
- EMEND (aprepitant) and AKYNZEO (netupitant/palonosetron) have several potential drug interactions. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4 and CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Please see the prescribing information for specific drugs affected and additional details.
- The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, while using doxylamine/pyridoxine, are not recommended (unless cleared to do so by the health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties, so should be used with caution in women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction.

DOSAGE AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
5-HT_3 Receptor Antagonists				
Dolasetron	Injection: 20 mg/mL vial Tablet: 50 mg 100 mg	<u>Prevention or treatment of postoperative nausea and/or vomiting:</u> Injection: 12.5 mg IV as a single dose 15 min before the cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment) <u>Prevention of cancer CINV:</u> Tablet: 100 mg within one hour before chemotherapy	<u>Prevention or treatment of postoperative nausea and/or vomiting:</u> Injection: 0.35 mg/kg IV, with a maximum dose of 12.5 mg, given as a single dose 15 min before the cessation of anesthesia or as soon as nausea or vomiting presents <u>Prevention of cancer CINV:</u> Tablet: 1.8 mg/kg within one hour before chemotherapy, up to a maximum of 100 mg	Dolasetron injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. When the injection is administered orally, the oral dosage in children is 1.2 mg/kg up to a maximum 100 mg dose within two hours before surgery.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
				The prepared solution may be kept up to two hours at room temperature before use.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Granisetron	Extended-release subcutaneous injection: 10 mg/0.4 mL per kit; supplied as cartons of six kits. Injection: 0.1 mg/mL 1 mg/mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours	Emetogenic chemotherapy: Tablet: two 1 mg tablets once daily up to one hour before chemotherapy; or one-1 mg tablet twice daily, given as one tablet one hour before chemotherapy and one tablet 12 hours later Prevention of CINV: Injection: 10 mcg/kg IV within 30 min before the initiation of chemotherapy and only on the days chemotherapy is given Prevention of n/v with moderately emetogenic chemotherapy and/or highly emetogenic chemotherapy regimens of up to five consecutive days duration: Transdermal patch: apply one patch to the upper outer arm a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Prevention of n/v with moderately emetogenic chemotherapy and/or anthracycline and cyclophosphamide combination chemotherapy regimens: Extended-release injection: 10 mg subcutaneous injection at least 30 minutes before the start of emetogenic chemotherapy on Day 1; do not administer more frequently than once every 7 days. Radiation (TBI or fractionated abdominal radiation): Tablet: two 1 mg tablets once daily within one hour of radiation Prevention of PONV: Injection: 1 mg IV before induction of anesthesia or immediately before reversal of anesthesia Treatment of PONV: Injection: 1 mg IV	Prevention of CINV: Injection: 10 mcg/kg IV	Extended-release subcutaneous injection: Intended for administration by a healthcare provider by a slow, sustained injection over 20 to 30 seconds; administer in skin of the back of the upper arm or in the skin of the abdomen at least 1 inch away from the umbilicus; do not substitute non-kit components for any of the components from the kit for administration. Transdermal patch: The patch may be worn for up to seven days depending on the duration of the chemotherapy regimen.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Ondansetron	Injection: 2 mg/mL vials (single- and multi-use vials) ODT: 4 mg 8 mg Oral soluble film: 4 mg 8 mg Oral solution: 4 mg/5 mL Tablet: 4 mg 8 mg 16 mg 24 mg	<u>Prevention of n/v associated with highly emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet: 24 mg given as three 8 mg tablets/films administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2 <u>Prevention of n/v associated with initial and repeat courses of emetogenic chemotherapy</u>: Injection: three 0.15 mg/kg doses IV up to a maximum of 16 mg per dose; the first dose is given over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given four and eight hours after the first dose <u>Prevention of n/v associated with moderately emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) oral solution given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose eight hours later; then twice daily (every 12 hours) for one to two days after the completion of chemotherapy <u>Prevention of n/v associated With radiotherapy (TBI):</u> ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before each fraction of radiotherapy administered each day <u>Prevention of n/v associated with radiotherapy (single high-dose fraction radiotherapy to the abdomen)</u>: ODT, oral soluble film, oral	<u>Prevention of n/v associated with initial and repeat courses of emetogenic chemotherapy</u>: Injection: three 0.15 mg/kg doses IV up to a maximum of 16 mg per dose; the first dose is given over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given four and eight hours after the first dose <u>Prevention of n/v associated with moderately emetogenic cancer chemotherapy</u>: ODT, oral soluble film, oral solution, tablet (patients ≥12 years of age): same dosing as adults ODT, oral soluble film, oral solution, tablet (patients four to 11 years of age): one 4 mg tablet, ODT, soluble film, or 5 mL (4 mg) of oral solution given three times daily with the first dose given 30 min before the start of emetogenic chemotherapy and subsequent doses four and eight hours later; then three times daily (every eight hours) for 1 to 2 days after completion of chemotherapy <u>Prevention of PONV:</u> Injection: a single 0.1 mg/kg dose for patients weighing ≤40 kg; or a single 4 mg dose for patients weighing >40 kg, administered over 2 to 5 min immediately prior to or following anesthesia induction, or	Oral soluble film: each soluble film should be allowed to completely dissolve before administering any subsequent film.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
		solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before radiotherapy, with subsequent doses every eight hours after the first dose for one to two days after completion of radiotherapy <u>Prevention of n/v associated with radiotherapy (daily fractionated radiotherapy to the abdomen)</u>: ODT, oral soluble film, oral solution, tablet: one 8 mg tablet, ODT, soluble film, or 10 mL (8 mg) of oral solution given one to two hours before radiotherapy, with subsequent doses every eight hours after the first dose for each day radiotherapy is given <u>Prevention of PONV:</u> Injection: 4 mg (undiluted) IV over two to five minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within two hours after surgery; OR 4 mg (undiluted) IM as a single dose ODT, oral soluble film, oral solution, tablet: 16 mg given as two 8 mg tablets, ODT tablets, soluble films, or 20 mL (16 mg) of oral solution one hour before induction of anesthesia	postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery	
Palonosetron	Injection: 0.25 mg/5 mL (single-use vial)	<u>Prevention of CINV:</u> Injection (adults): a single 0.25 mg IV dose given over 30 seconds, approximately 30 minutes before the start of chemotherapy <u>Prevention of PONV:</u> Injection: a single 0.075 mg IV dose given over 10 seconds immediately before the induction of anesthesia	Injection (pediatric): a single 20 mcg/kg (max 1.5 mg) IV dose given over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	Not applicable

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
Substance P/NK_1 Receptor Antagonists				
Aprepitant	Capsule: 40 mg 80 mg 125 mg Combination pack (capsule): 80 and 125 mg Oral suspension: 125 mg/5 mL (after mixing)	<u>Prevention of CINV in adults and pediatric patients ≥ 12 years:</u> Capsule: 125 mg one hour prior to chemotherapy treatment on day one and 80 mg once daily on days two and three Oral suspension for adults who are unable to swallow capsules: 125 mg one hour prior to chemotherapy treatment on day one and 80 mg once daily on days two and three <u>Prevention of PONV:</u> Capsule: 40 mg within three hours prior to induction of anesthesia	<u>Prevention of CINV in pediatric patients 6 months to < 12 years:</u> Oral suspension: 3 mg/kg (maximum 125 mg) on day one, 2 mg/kg (maximum 80 mg) on days two and three	Aprepitant can be given with or without food Aprepitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Fosaprepitant	Injection: 150 mg/mL single-use vial	<u>Prevention of cancer CINV:</u> Highly Emetic Chemotherapy (HEC Single Dose Regimen): 150 mg administered on day one 30 minutes prior to chemotherapy Moderately Emetic Chemotherapy: 150 mg IV about 30 minutes before chemotherapy	Not applicable	Fosaprepitant is administered IV as a 20 to 30 minute infusion Fosaprepitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Rolapitant	Tablet: 90 mg	<u>Prevention of delayed CINV, including, but not limited to, highly emetogenic chemotherapy:</u> 180 mg given approximately 1 to 2 hours prior to chemotherapy on day 1	Not applicable	Rolapitant is given as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist
Combination product				
Palonosetron/ netupitant	Capsule: 300 mg netupitant/ 0.5 mg palonosetron	<u>Prevention of CINV, including, but not limited to, highly emetogenic chemotherapy:</u> One capsule given 1 hour prior to the start of chemotherapy	Not applicable	This combination product is part of a regimen that includes a corticosteroid
Miscellaneous				
DICLEGIS	Delayed-release tablet: 10 mg doxylamine succinate/ 10	Take two tablets by mouth daily at bedtime. If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose	Not applicable	Should be taken on an empty stomach with a glass of water

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose & Dosing Considerations	Administration Considerations
	mg pyridoxine HCl	of four tablets daily (one in the morning, one mid-afternoon, and two at bedtime)		Swallow tablets whole (do not crush, chew, or split)
BONJESTA	Extended-release tablet: 20 mg doxylamine succinate/ 20 mg pyridoxine HCl	On day one, take one tablet at bedtime. On day two, if symptoms are not adequately controlled, the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum dose is two tablets daily, one in the morning and one at bedtime	Not applicable	Should be taken on an empty stomach with a glass of water Swallow tablets whole (do not crush, chew, or split)

Abbrv: CINV=chemotherapy-induced nausea and vomiting, IM=intramuscular, IV=intravenous, ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, TBI=total body irradiation
*Supplied by multiple generic manufacturers in single-use and multi-use vial sizes.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
5-HT$_3$ Receptor Antagonists					
Dolasetron	No dose adjustment required.	No dose adjustment required in children. Approved for use in children two to 16 years (based on pharmacokinetic data in adults). Not studied in patients <2 years.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Granisetron	No dose adjustment required.	No dose adjustment required. Injection approved for CINV in children two to 16 years. Granisetron injection not studied in patients <2 years. Extended-release injection, ODT, tablet, transdermal patch: not studied in pediatrics.	Renal dose adjustment not required. Extended-release injection: avoid in patients with severe renal impairment (CrCl < 30mL/min); for patients with moderate renal impairment (30 to 59	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution. Extended-release injection: no available data on the use in pregnant women.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
			mL/min), administer not more frequently than once every 14 days.		
Ondansetron	No dose adjustment required.	Injection (6 months to 18 years for prevention of CINV): weight-based dosing up to 16 mg per dose three times daily. Injection (one month to 12 years for prevention of PONV): single 0.1 mg/kg for patients ≤40 kg or a single 4 mg dose for patients >40 kg. Injection: not studied in patients <1 month of age. ODT, oral solution, oral soluble film, tablet (≥12 years): no dose adjustment required. ODT, oral solution, oral soluble film, tablet (four to 11 years for moderately emetogenic CINV): half the adult dose. ODT, oral solution, oral soluble film, tablet: not studied in patients <4 years or in the prevention of CINV due to highly emetogenic chemotherapy, PONV, or RINV.	Renal dose adjustment not required.	In severe hepatic impairment (Child-Pugh score ≥10), do not exceed a single 8 mg dose on the first day of chemotherapy or a total daily dose of 8 mg. There is no experience beyond first-day administration in these patients.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Palonosetron	No dose adjustment required.	Injection (1 month to <17 years for prevention of CINV): a single weight-based dose (max 1.5 mg) before the start of chemotherapy	Renal dose adjustment not required.	Hepatic dose adjustment not required.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Substance P/NK_1 Receptor Antagonists					
Aprepitant	Use caution when	Oral suspension (6 months to <12 years for	Renal dose adjustment	Use with caution in	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	dosing elderly patients.	prevention of CINV): a single weight-based dose on days 1, 2, and 3 given 1 hour before chemotherapy	not required.	patients with severe hepatic impairment (Child-Pugh score >9).	Unknown whether excreted in breast milk; use with caution.
Fosaprepitant	Use caution when dosing elderly patients.	Safety and efficacy in children have not been established.	Renal dose adjustment not required.	Use with caution in patients with severe hepatic impairment (Child-Pugh score >9).	Unclassified† Unknown whether excreted in breast milk; use with caution.
Rolapitant	No dose adjustment required.	Safety and efficacy in children have not been established.	Renal dose adjustment required.	Avoid use in patients with severe hepatic impairment (Child-Pugh class C).	Unclassified† Unknown whether excreted in breast milk; use with caution
Combination product					
Palonosetron/ netupitant)	Use caution when dosing elderly patients.	Safety and efficacy in children have not been established.	No dose adjustment is needed for mild to moderate renal impairment; avoid use in severe impairment.	No dose adjustment is needed for mild to moderate hepatic impairment (Child-Pugh score 5 to 8); avoid use in severe impairment.	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
Miscellaneous					
Doxylamine succinate/ pyridoxine HCl	Not studied in the elderly population	Safety and efficacy in children have not been established.	Not studied in renal dysfunction	Not studied in hepatic dysfunction	Pregnancy Category A (DICLEGIS) Unclassified† (BONJESTA) Women should not breastfeed while using doxylamine succinate/ pydridoxine HCl

Abbrv: CINV=chemotherapy-induced nausea and vomiting, ODT=orally disintegrating tablet, PONV=postoperative nausea and vomiting, RINV=radiation-induced nausea and vomiting

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

*****Pregnancy Category B=No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery.
- Treatment of CINV or RINV generally involves the use of multiple agents that affect different receptor types, such as 5-HT_3 receptor antagonists, substance P/NK_1 receptor antagonists, and corticosteroids (AGA, 2001; Herrstedt et al, 2016; Hesketh et al, 2016; Roila et al, 2010).
- Choice of agents generally depends upon the relative emetogenic potential of the chemotherapy regimen (AGA, 2001; Hesketh et al, 2016; Roila et al, 2010).
- The 5-HT_3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV (AGA, 2001; Gupta et al, 2016; Herrstedt et al, 2016; Hesketh et al, 2016; Gan et al, 2014; Roila et al, 2010).
- ALOXI (palonosetron) has a longer half-life than the other 5-HT_3 receptor antagonists, and single-dose therapy with ALOXI (palonosetron) is reported to be more effective than other medications in the class, particularly at preventing delayed emesis (Aapro et al, 2005; Billio et al, 2010; Botrel et al, 2011; Dong et al, 2011; Eisenberg et al, 2003; Gralla et al, 2003; Kaushal et al, 2010; Kovacs et al, 2016; Likun et al, 2011; Simino et al, 2016; Suzuki et al, 2016).
- In addition to CINV, granisetron and ZOFRAN (ondansetron) are also indicated for the treatment of RINV and have been shown to be equally effective (Billio et al, 2010; Dabbous et al, 2010; Erhan et al, 2008; Jain et al, 2009; Spitzer et al, 2000).
- Treatment with EMEND (aprepitant) has been shown to be effective for the prevention of CINV in combination with various 5-HT_3 receptor antagonists and dexamethasone (Hesketh et al, 2016; Herrington et al, 2008; Grunberg et al, 2011; Rapoport et al, 2010; Yeo et al, 2009; Herrstedt et al, 2005; Warr et al, 2005; Gralla et al, 2005).
- The fixed-dose combination AKYNZEO (palonosetron and netupitant) + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following moderately emetogenic chemotherapy (Aapro et al, 2014); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (Gralla et al, 2014).
- The addition of EMEND (aprepitant) to a 5-HT_3 receptor antagonist and dexamethasone regimen resulted in a greater proportion of patients achieving complete response (Gralla et al, 2005; De Wit et al, 2004; Poli-Bigelli et al, 2003; Hesketh et al, 2003; Martin et al, 2003).
- A 2016 meta-analysis found that when compared to other 5-HT3 antagonists and NK_1 antagonists, EMEND (aprepitant) reduces incidence of PONV, and need for rescue medications (Singh et al, 2016).
- DICLEGIS and BONJESTA are fixed dose combination drug products of doxylamine succinate and pyridoxine HCl , and both are indicated for the treatment of NVP in women who do not respond to conservative management. The combination of these agents was previous available in the United States under the name brand BENDECTIN®.
- The 2016 ASCO antiemetic guidelines recommend a three-drug combination of a NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone as first-line therapy for the prevention of CINV due to highly emetogenic chemotherapy agents. For moderately emetogenic agents, a two-drug combination of ALOXI (palonosetron) plus dexamethasone is recommended (Hesketh et al, 2016).
- A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (Gupta et al, 2016).
- The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first line pharmacologic therapy (ACOG, 2015).
- EMEND (aprepitant) has been considered superior to a 5-HT_3 receptor antagonist in the prevention of delayed emesis induced by moderately emetogenic chemotherapy in breast cancer patients receiving a combination of anthracycline and cyclophosphamide treated with aprepitant, a 5-HT_3 antagonist, and dexamethasone; therefore, EMEND (aprepitant) should be used to prevent delayed n/v (Roila et al, 2010).
- The 5-HT_3 receptor antagonists are generally very well tolerated. There is a warning and general precaution for ANZEMET (dolasetron) regarding the risk of arrhythmias. ZOFRAN (ondansetron) and granisetron have QTc prolongation as a general precaution, but the incidence of ECG changes has been less than 1%. In addition, the development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists.
- Granisetron and ZOFRAN (ondansetron) are the only 5-HT_3 receptor antagonists that are available generically.
- All of the 5-HT_3 receptor antagonists are available as injections and all but ALOXI (palonosetron) are currently available as oral products. Granisetron is also available in a transdermal patch (SANCUSO) and extended-release injection (SUSTOL).

Table 4. Advantages and Disadvantages of Antiemetics – 5-HT_3 Receptor Antagonists

Drug	Advantages	Disadvantages
5-HT_3 Receptor Antagonists		
Dolasetron	• Approved for use in children ages two to 16 years of age. • Dolasetron injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients. • Pregnancy category B. • FDA indication for PONV.	• Not available generically. • Adverse effects of QTc prolongation.
Granisetron	• Injection products approved for use in children two to 16 years of age. • Available in different formulations including injection, tablets, and transdermal patch. • Oral tablets and injection are available generically. • Pregnancy category B. • SANCUSO patch has a long duration of effect, allowing for extended coverage of n/v as well as n/v that prevents the administration of oral therapies. • FDA indication for RINV (tablet) and prevention of PONV (injection).	• SANCUSO patch and SUSTOL extended-release injection are not available generically.
Ondansetron	• Safety and efficacy in pediatrics as young as 6 months. • Available in different formulations including injection, tablets, oral soluble film, and oral solution. • Available generically in injection, oral solution, and oral tablet formulations. • Pregnancy category B. • Oral formulations have FDA indication for RINV and PONV.	• ZUPLENZ not available generically. • Adverse effects of QTc prolongation.
Palonosetron	• Safety and efficacy in children ages 1 month to <17 years for prevention of CINV. • Pregnancy category B. • FDA indication for PONV. • Longest half-life (40 hours) of the 5-HT_3 receptor antagonists.	• Not available generically. • Only available as an injection.
Substance P/NK_1 Receptor Antagonists		
Aprepitant, fosaprepitant	• Available in different formulations including injection, capsules, and oral suspension. • Aprepitant capsules are available generically. • FDA indication for prevention of PONV (capsule).	• Aprepitant oral suspension and fosaprepitant are not available generically.
Rolapitant	• None	• Only approved for delayed CINV. • Only available as a tablet. • Not available generically. • Safety and effectiveness have not been established in children <18 years of age.
Combination Product		
Palonosetron/ netupitant	• Only available oral product containing a 5-HT_3 receptor antagonist and substance P/NK_1 receptor antagonist.	• Not available generically. • Safety and effectiveness have not been established in children <18 years of age. • Pregnancy Category C. • Only available as a capsule.

Drug	Advantages	Disadvantages
Miscellaneous		
Doxylamine succinate/pyridoxine HCl	• Only FDA-approved agent for the treatment of nausea and vomiting of pregnancy. • Initial dosing allows for once daily dosing.	• Available as individual components. • Only available as a tablet.

Abbrv: CINV=chemotherapy-induced nausea and vomiting, FDA=Food and Drug Administration, PONV=postoperative nausea and vomiting, RINV=radiation-induced nausea and vomiting

(Clinical Pharmacology, 2017; Micromedex, 2017)

REFERENCES

- Aapro MA, Macciocchi A, Gridelli C. Palonosetron improves prevention of CINV in elderly patients. J Supp Oncology. 2005;3(5):369-74.
- Aapro M, Rugo H. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol. 2014;25:1328-33.
- AKYNZEO prescribing information. Eisai, Inc. Woodcliff Lake, NJ. December 2015.
- ALOXI injection prescribing information. OSO Biopharmaceuticals for Eisai Inc. Albuquerque, NM. December 2015.
- The American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126:687-688
- American Gastroenterological Association [AGA] medical position statement: nausea and vomiting. Gastroenterology.2001;120(1):261-2.
- ANZEMET injection prescribing information. Sanofi-Aventis U.S. Bridgewater, NJ. September 2014.
- ANZEMET tablets prescribing information. Sanofi-Aventis U.S. Bridgewater, NJ. September 2014.
- Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006272.
- Boccia RV, Gordan LN, Clark G, et al. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced n/v associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study. Support Care Cancer. 2011;19:1609-17.
- BONJESTA prescribing information. Duchesnay, Inc. Bryn Mawr, PA. November 2016.
- Botrel TEA, Clark OAC, Clark L, et al. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT_3R) in preventing chemotherapy-induced n/v (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. Support Care Cancer. 2011;19:823-32.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available by subscription at: http://www.clinicalpharmacology.com. Accessed March 21, 2017.
- Dabbous AS, Jabbour-Khoury SI, Nasr VG, et al. Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery. Middle East J Anaesthesiol. 2010;20(4):565-70.
- del Giglio A, Soares HP, Caparroz C, et al. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced n/v. Results of a meta-analysis of randomized controlled trials. Cancer. 2000;89:2301-8.
- Dempsey CL, Coop AJ, Shillington A, et al. Antiemetic effectiveness of ondansetron and granisetron in patients with breast cancer treated with cyclophosphamide. Am J Health-Syst Pharm. 2004;61:781-6.
- De Wit R, Herrstedt J, Rapoport B. The oral NK (1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. Eur J Cancer. 2004; 40(3):403-10.
- DICLEGIS prescribing information. Duchesnay, Inc. Bryn Mawr, PA. April 2013.
- Dong X, Huang J, Cao R, et al. Palonosetron for prevention of acute and delayed n/v in non-small-cell lung carcinoma. Med Oncol. 2011;28:1425-29.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 21, 2017.
- Eberhart LH, Morin AM, Hoerle S, et al. Droperidol and dolasetron alone or in combination for prevention of PONV after vitrectomy. Ophthalmology. 2004;111:1569-75.
- Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced n/v with palonosetron, a pharmacologically novel 5-HT_3 receptor antagonist. Cancer. 2003;98:2473-82.
- EMEND capsules and oral suspension prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. January 2017.
- EMEND for injection prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. February 2016.
- Erhan Y, Erhan E, Aydede H, et al. Ondansetron, granisetron, and dexamethasone compared for the prevention of PONV in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2008;22:1487-92.
- Feyer P, Jordan, K. Radiotherapy-induced nausea and vomiting: prophylaxis and treatment. In: Basow DS, editor. Massachusetts: UpToDate; 2016. Available by subscription from: http://www.uptodate.com/utd/index.do. Accessed March 21, 2017.
- Gan TJ, Coop A, Philip BK, et al. A randomized, double-blind study of granisetron plus dexamethasone vs ondansetron plus dexamethasone to prevent PONV in patients undergoing abdominal hysterectomy. Anesth Analg. 2005;101:1323-9.
- Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118:85-113.
- George RB, Allen TK, Habib AS. Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: a systematic review and meta-analysis. Anesth Analg. 2009;109(1):174-82.
- Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer. 2009;52:242-7.
- Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol. 2014;25(7):1333-9.

- Gralla R, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5-HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two Phase III randomized clinical trials. Cancer. 2005;104(4):864-8.
- Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced n/v following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncology. 2003;14:1570-7.
- Granisetron injection prescribing information. Fresenius Kabi, USA, LLC. Lake Zurich, IL. May 2015.
- Granisetron tablets prescribing information. Roxane Laboratories, Inc. Columbus, OH. October 2015.
- Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. J Clin Oncol. 2011;29:1495-501.
- Grunberg SM, Dugan M, Muss H, et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer. 2009;17:589-94.
- Gupta R and Soto R. Prophylaxis and management of postoperative nausea and vomiting in enhanced recovery protocols: expert opinion statement from the American Society for Enhanced Recovery (ASER). Perioperative Medicine. 2016;5(4):1-2.
- Herrington J, Jaskiewicz, Song J. Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Cancer. 2008;112:2080-7.
- Herrstedt J, Muss H, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer. 2005;104(7):1548-55.
- Herrstedt J, Roila F, Warr D, et al. 2016 Updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. Support care cancer. 2016. doi:10.1007/s00520-016-3313-0. [Epub ahead of print].
- Hesketh PH, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol. 2016;34(4):381-6.
- Hesketh PJ and Sanz-Altamira P. Aprepitant, dexamethasone, and palonosetron in the prevention of doxorubicin/cyclophosphamide-induced nausea and vomiting. Support Care Cancer. 2012;20:653–6.
- Hesketh PJ, Grunberg SM, Gralla RJ. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003; 21 (22):4112-9.
- Hesketh PJ. Pathophysiology and prediction of chemotherapy-induced nausea and vomiting. In: Post TW (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017[a]. Available by subscription at: http://www.uptodate.com/home . Accessed March 24, 2017.
- Hesketh PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting in adults. In: Post TW (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2017[b]. Available by subscription at: http://www.uptodate.com/home . Accessed March 24, 2017.
- Jain V, Mitra JK, Rath GP, et al. A randomized, double-blind comparison of ondansetron, granisetron, and placebo for prevention of PONV after supratentorial craniotomy. J Neurosurg Anesthesiol. 2009;21:226-30.
- Jaing T, Tsay P, Hung I, et al. Single-dose oral granisetron vs multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic leukemia. Pediatr Hemato Onc. 2004;21:227-35.
- Jordan K, Kinitz I, Voigt W, et al. Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. Eur J Cancer. 2009;45:1184-7.
- Kalaycio M, Mendez Z, Pohlman B, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of n/v after high-dose chemotherapy. J Cancer Res Clin Oncol. 1998;124:265-9.
- Karamanlioglu B, Turan A, Memis D, et al. Comparison of oral dolasetron and ondansetron in the prophylaxis of PONV in children. Eur J Anesth. 2003;20:831-5.
- Kaushal J, Gupta MC, Kaushal V, et al. Clinical evaluation of two antiemetic combinations palonosetron dexamethasone vs ondansetron dexamethasone in chemotherapy of head and neck cancer. Singapore Med J. 2010;51(11):871-75.
- Koren G et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. American Journal of Obstetrics and Gynecology. 2010 Dec;2013:571.e1-7.
- Koren G et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized controlled trial. BMC Pregnancy and Childbirth. 2015;15(59):1-6.
- Kovacs G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova E. Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study. Lancet Oncol. 2016;17(3):332-344.
- Lacerda JF, Martins C, Carmo JA, et al. Randomized trial of ondansetron, granisetron, and tropisetron in the prevention of acute n/v. Transplantation Proc. 2000;32:2680-1.
- Likun Z, Xiang J, Yi B, et al. A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced n/v in adults. The Oncologist. 2011;16:207-16.
- Lofters WS, Pater JL, Zee B, et al. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed n/v due to moderately emetogenic chemotherapy. J Clin Oncol. 1997;15:2966-73.
- Longstreth GF. Approach to the adult with n/v. In: Basow DS, editor. UpToDate. Waltham (MA): UpToDate; 2016. Available by subscription from: http://www.uptodate.com/utd/index.do. Accessed March 21, 2017.
- Mannix K. Palliation of n/v in malignancy. Clin Med. 2006; 6:144-7.
- Martin A, Carides A. Functional relevance of antiemetic control. Experience using the FLIE questionnaire in a randomized study of the NK-1 antagonist aprepitant. Eur J Cancer. 2003;39(10):1395-401.
- Massa E, Astara G, Madeddu C, et al. Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced n/v following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: comparison between elderly and non-elderly patient response. Clinical reviews in Oncology/Hematology. 2009;70:83-91.
- Meyer TA, Roberson CR, Rajab MH, et al. Dolasetron vs ondansetron for the treatment of postoperative n/v. Anesth Analg. 2005;100:373-7.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2017. Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed March 21, 2017.
- National Cancer Institute: PDQ® Nausea and Vomiting. Bethesda, MD: National Cancer Institute. Updated March 14, 2017. Available at: http://cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional. Accessed March 21, 2017.

- Ondansetron prescribing information. Dr. Reddy's Laboratories Limited. Bachupally – 500 090 India. October 2014.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 21, 2017.
- Orchard PJ, Rogosheske J, Burns L, et al. A prospective randomized trial of the antiemetic efficacy of ondansetron and granisetron during bone marrow transplantation. DBMT. 1999;386-93.
- Phillips RS, Friend AJ, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database of Systematic Reviews. 2016, Issue 2. Art. No.: CD007786.
- Poli-Bigelli S, Rodrigues-Pereira J, et al. Addition of the neurokinin 1 receptor aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer. 2003; 97(12):3090-8.
- Raftopoulos H, Cooper W, O'Boyle E, Gabrail N, Boccia R, Gralla RJ. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. Support Care Cancer. 2015[a];23(3):723-32.
- Raftopoulos H, Boccia R, Cooper W, O'Boyle E, Gralla RJ. Slow-release granisetron (APF530) versus palonosetron for chemotherapy-induced nausea/vomiting: analysis by American Society of Clinical Oncology emetogenicity criteria. Future Oncol. 2015[b];11(18):2541-51.
- Rapoport B, Schwartzberg L, Chasen M, et al. Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting over multiple cycles of moderately or highly emetogenic chemotherapy. Eur J Cancer. 2016;57:23-30.
- Rapoport BL, Chasen MR, Gridelli C et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015;16(9):1079-89.
- Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. 2010;18:423-31.
- Roila F, Herrstedt J, Aapro M, et al. Clinical Practice Guidelines: Guidelines update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced n/v: results of the Perugia consensus conference. Annals of Oncology. 2010;21(Supp 5):V232-43.
- Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. J Clin Oncol. 2014; 32(2):101-6.
- Salvo N, Doble B, Khan L, et al. Prophylaxis of radiation-induced n/v using 5-hydroxytryptamine-3 serotonin receptor antagonists: a systematic review of randomized trials. Int J Radiation Oncologu Biol Phys. 2012;82(1):408-17.
- SANCUSO prescribing information. 3M Delivery Systems for Prostrakan Inc. St. Paul, MN. September 2015.
- Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol. 2015;16(9):1071-8.
- Simino GP, Marra LP, Andrade EI, et al. Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT3RAs) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. Expert Rev Clin Pharmacol. 2016:1-12.
- Singh PM, Borle A, Rewari V, et al. Aprepitant for postoperative nausea and vomiting: a systematic review and meta-analysis. Postgrad Med J. 2016;92(1084):87-98.
- Singhal AK, Kannan S, Gota VS. 5-HT3 antagonists for prophylaxis of postoperative n/v in breast surgery: a meta-analysis. Journal of Postgraduate Medicine. 2012;58(1):23-31.
- Smith JA, Refuerzo, JS, Ramin SM. Treatment and outcome of nausea and vomiting of pregnancy. UpToDate Web site. 2017. www.uptodate.com. Accessed March 20, 2017.
- Spitzer TR, Friedman CJ, Bushnell W, et al. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of n/v in patients receiving hyperfractionated total body irradiation. Bone Marrow Transplantation. 2000;26:203-10.
- SUSTOL prescribing information. Heron Therapeutics. Redwood City, CA. August 2016.
- Suzuki K, Yamanaka T, Hashimoto H, et al. Randomized, double-blind, phase III trial of palonosetron versus granisetron in the triplet regimen for preventing chemotherapy-induced nausea and vomiting after highly emetogenic chemotherapy: TRIPLE study. Ann Oncol. 2016;27(8):1601-1606.
- Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative n/v prophylaxis. Clinical Therapeutics. 2012;34(2):282-94.
- VARUBI prescribing information. Tesaro, Inc. Waltham, MA. September 2015.
- Walker JB. Efficacy of single-dose intravenous dolasetron vs ondansetron in the prevention of postoperative n/v. Clin Ther. 2001;23(6):932-8.
- Warr DG, Hesketh PJ, Gralla R. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol. 2005; 23(12):2822-30.
- White PF, Tang J, Hamza MA, et al. The use of oral granisetron vs intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. Anesth Analg. 2006;102:1387-93.
- Xiong C, Liu G, Ma R, et al. Efficacy of palonosetron for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. Can J Anaesth. 2015;62(12):1268-78.
- Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat. 2009;113:529-35.
- ZOFRAN injection prescribing information. GlaxoSmithKline. Research Triangle Park, NC. September 2014.
- ZOFRAN tablets, orally disintegrating tablets, oral solution prescribing information. GlaxoSmithKline. Research Triangle Park, NC. October 2016.
- ZUPLENZ prescribing information. Monosol RX, LLC for Galena Biopharma Inc. Warren, NJ. January 2017.

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Therapeutic Class Overview
Oral Anticoagulants

INTRODUCTION

- The oral anticoagulants include ELIQUIS® (apixaban), PRADAXA® (dabigatran), SAVAYSA® (edoxaban), XARELTO® (rivaroxaban), and warfarin (COUMADIN®, JANTOVEN®).
- Warfarin has been the principal oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy. However, warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- The four target specific oral anticoagulants (TSOACs), PRADAXA, XARLETO, SAVAYSA, and ELIQUIS, are all indicated for the reduction of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), otherwise known as events caused by a venous thromboembolism (VTE). PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE. PRADAXA, XARELTO, and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing hip replacement surgery and XARELTO and ELIQUIS have further indications for knee replacement surgery.
- Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the U.S. affecting approximately 2.7 to 6.1 million people in 2010. AF has been associated with death either directly or cited as an underlying cause contributing to mortality. Stroke is the most concerning complication of AF. Before the widespread use of anticoagulants, and after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke (Benjamin et al, 2017). Approximately 5 to 8% of patients who require percutaneous coronary intervention (PCI) with stents have AF (Gibson et al, 2016).
- In patients with AF, oral anticoagulants are recommended for those who are at an intermediate or greater risk of stroke and selection should be based on individual patient characteristics (Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017).
- VTE encompasses both DVT and PE. The precise number of people affected is unknown, but it is estimated to affect ~900,000 US patients (CDC, 2017). Of those who suffer a DVT, approximately a third will have a recurrence within 10 years. Knee and hip replacement surgeries are associated with a high risk of VTE, which can lead to recurrent VTE events as well as post-thrombotic syndrome, and PE, which can be fatal. Without anticoagulant therapy, 40% to 50% of patients undergoing hip replacement surgery suffer VTE. This rises to 70% to 80% in hip fracture (American Academy of Orthopaedic Surgeons [AAOS], 2011; Guyatt et al, 2012; Kearon et al, 2016).
- Pharmacological anticoagulants available for the treatment of VTE (not due to orthopedic surgery) include parenteral anticoagulation (low molecular weight heparin [LMWH], fondaparinux, or intravenous [IV] or subcutaneous [SC] unfractionated heparin [UFH]) typically administered with warfarin, or the TSOACs (XARELTO, ELIQUIS, PRADAXA, or SAVAYSA) (Guyatt et al, 2012; Kearon et al, 2016; Micromedex® 2.0, 2017).
- Thromboprophylaxis is recommended to prevent VTE in patients undergoing total hip or knee replacement. Pharmacological anticoagulants available for the prophylaxis of VTE after orthopedic surgery include aspirin, LMWHs, warfarin, PRADAXA, and factor (F) Xa inhibitors (ARIXTRA® [fondaparinux], XARELTO, or ELIQUIS) (AAOS, 2011; Guyatt et al, 2012).
- The oral anticoagulants work through varied mechanisms of action. XARELTO, SAVAYSA and ELIQUIS are selective FXa inhibitors, while PRADAXA is a direct thrombin inhibitor. Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors. Vitamin K, therefore, serves as a reversal agent for warfarin.
    - In 2015, the first TSOAC reversal agent, PRAXBIND® (idarucizumab), was FDA-approved. PRAXBIND is indicated for the reversal of PRADAXA's anticoagulation effects as needed for emergency surgery, urgent procedures, and in life-threatening or uncontrolled bleeding (PRAXBIND prescribing information, 2015).
    - There are no specific antidotes for ELIQUIS, SAVAYSA or XARELTO; however, ANDEXXA™ (andexanet alfa) is an investigational agent that was submitted to the FDA for approval. Studies currently support use with ELIQUIS and XARELTO. In August 2016, the FDA issued a complete response letter (CRL) requesting additional information. Portola Pharmaceuticals have expressed they have plans to submit the biologics licensing application after deficiencies have been addressed in the CRL (Portola Pharmaceuticals press release, 2017).
    - Another antidote, ciraparantag, is an intravenously administered small molecule which has demonstrated complete and sustained reversals of SAVAYSA and LOVENOX without rebound anticoagulation in Phase 2 trials

and the reversal of PRADAXA, XARELTO, ELIQUIS, fondaparinux, and heparin ex vivo (Perosphere press release, 2016).

- Medispan class: Anticoagulants; Thrombin Inhibitors; Coumarin Anticoagulants; Direct FXa Inhibitors

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ELIQUIS (apixaban)	Pfizer	12/28/2012	-
PRADAXA (dabigatran)	Boehringer Ingelheim	10/19/2010	-
SAVAYSA (edoxaban)	Daiichi Sankyo	01/08/2015	-
XARELTO (rivaroxaban)	Janssen	07/01/2011	-
COUMADIN*, JANTOVEN* (warfarin)	Various	06/08/1954	✔

*Generic available in at least one dosage form or strength

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ELIQUIS (apixaban)	PRADAXA (dabigatran)	SAVAYSA (edoxaban)	XARELTO (rivaroxaban)	COUMADIN JANTOVEN (warfarin)†
Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement					✔
Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE)					✔
Reduce the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI					✔
Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)	✔	✔	✔ ‡	✔	
Prophylaxis of deep vein thrombosis (DVT), which may lead to PE, in patients undergoing knee (TKR) or hip (THR) replacement surgery	✔			✔	
Prophylaxis of DVT and PE in patients undergoing THR surgery		✔			
Treatment of DVT and PE	✔	✔ *	✔ *	✔	
Reduction in the risk of recurrence of DVT and PE following initial therapy	✔	✔		✔	

*Prior to treatment, patients should have been treated with parenteral anticoagulant for 5 to 10 days.
†Limitation of use: Warfarin has no direct effect on an established thrombus, nor does it reverse ischemic tissue damage.
‡Not indicated in NVAF patients with CrCL > 95 mL/min due to increased rates of ischemic stroke.

(Prescribing information: COUMADIN, 2016; ELIQUIS, 2016; JANTOVEN, 2011; PRADAXA, 2015; SAVAYSA, 2016; XARELTO, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Warfarin has been the principal oral anticoagulant for more than 60 years and the evidence demonstrating the safety and efficacy in Food and Drug Administration (FDA)-approved indications is well established (Aguilar, 2005; Cundiff et al, 2006; DiNisio et al, 2012; Hutten, 2006; Lopes et al, 2013; Middeldorp et al, 2014; Salazar et al, 2010; Saxena, 2004; van der Heijden et al, 2001).
- There is no direct comparator evidence of the TSOACs; therefore, caution should be exercised when drawing conclusions based on indirect data.

Non-valvular Atrial Fibrillation:

- Four large randomized controlled trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48, and ROCKET AF) were the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively. Baseline populations varied for the PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials, with a mean proportion of 64%, 62%, 65%, and 55% time in therapeutic range (TTR) for warfarin patients and a mean baseline $CHADS_2$ score of 2.1, 2.1, 2.8, and 3.5, respectively (Connolly et al, 2009; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011).
- The primary efficacy endpoint was stroke or systemic embolism, in which the following outcomes were reported:
  - PRADAXA was superior (relative risk [RR] for PRADAXA150 mg twice daily vs warfarin, 0.66 [95% confidence interval {CI}, 0.53 to 0.82], P < 0.001).
  - ELIQUIS was superior (Hazard ratio [HR] for ELIQUIS 5 mg twice daily vs warfarin, 0.79 [95% CI, 0.66 to 0.95], P = 0.01).
  - SAVAYSA was non-inferior (HR for SAVAYSA 60 mg once daily vs warfarin, 0.79 [97.5% CI, 0.63 to 0.99], P < 0.001; HR for SAVAYSA 30 mg once daily vs warfarin, 1.07 [97.5% CI, 0.87 to 1.31], P = 0.005).
  - XARELTO was non-inferior (HR for XARELTO 15 to 20 mg once daily vs warfarin, 0.88 [95% CI, 0.75 to 1.03], P < 0.001).
- In terms of safety, the following important outcomes were observed in trials:
  - All TSOACs had fewer intracranial hemorrhages (ICH) compared to warfarin.
  - For major bleeds, ELIQUIS and SAVAYSA were superior to warfarin (ELIQUIS HR, 0.69 [95% CI, 0.6 to 0.8], P < 0.001; SAVAYSA HR, 0.8 [95% CI, 0.71 to 0.91], P < 0.001) and PRADAXA and XARELTO were non-inferior to warfarin (PRADAXA RR, 0.93 [95% CI, 0.81 to1.07], P = 0.31; XARELTO HR, 1.04 [95% CI, 0.9 to1.2], P = 0.58).
  - For gastrointestinal (GI) bleeds, warfarin significantly out-performed PRADAXA, SAVAYSA, and XARELTO (PRADAXA RR, 1.5 [95% CI, 1.19 to 1.89], P < 0.001; SAVAYSA HR, 1.23 [95% CI, 1.02 to 1.5], P = 0.03; XARELTO HR, not reported [incidence, XARELTO 3.2% vs warfarin 2.2%], P < 0.001); however, ELIQUIS had a similar incidence of GI bleeds when compared to warfarin (ELIQUIS HR 0.89 [95% CI, 0.7 to 1.15], P = 0.37).
- In 2016, the Alere INRatio device, which was used in the ROCKET AF trial, was recalled due to the potential for falsely low INR results. An article from the British Medical Journal (BMJ) suggested that an independent assessment of trial data should be performed. Researchers from the FDA, Bayer, Johnson and Johnson, and the Duke Clinical Research Institute performed a post-hoc data analysis and concluded that the recalled devices did not have significant clinical effects on the primary efficacy and safety trial outcomes. The FDA and European Medicines Agency (EMA) concluded that any incorrect INR measures would have marginal effects on the study outcomes; therefore, they should not impact the safety or benefit-risk balance of XARELTO (Cohen, 2016; EMA press release, 2016; FDA press release, 2016)
- Extension trials and additional analyses were conducted for the thromboprophylaxis of NVAF and the following key results were demonstrated:
  - After 2.3 years of PRADAXA treatment, slightly higher rates of stroke and systemic embolism, in addition to increased rates of major bleeding were observed in the long-term trial, RELAY-ABLE, compared to the RE-LY trial, particularly in the FDA-approved 150 mg dose (Connolly et al, 2013).
  - One pre-specified secondary analysis of the ENGAGE AF-TIMI 48 trial demonstrated ischemic cerebrovascular event rates were similar with SAVAYSA 60 mg and warfarin, whereas SAVAYSA 30 mg was less effective than warfarin (Giugliano et al, 2014). Another pre-specified analysis found that patients with genetic variants of CYP2C9 and VKORC1 derived a greater early safety benefit in bleeding rates with edoxaban over warfarin (Mega et al, 2015).
  - Data regarding GI adverse events and myocardial infarction with PRADAXA treatment have been conflicting. A subgroup analysis of GI adverse events found that PRADAXA demonstrated a statistically significant risk of non-

bleeding upper GI effects, which also resulted in a statistically larger proportion of patients discontinuing PRADAXA due to these effects (Bytzer et al, 2013).
  - A subgroup analysis demonstrated a nonsignificant increase in MI with PRADAXA compared to warfarin but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of PRADAXA were consistent in patients at higher and lower risk of myocardial ischemic events (Hohnloser et al, 2012). In contrast, a meta-analysis demonstrated that PRADAXA is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute VTE, ACS, short term prophylaxis of DVT) when compared against different controls (warfarin, enoxaparin, or placebo). It was not accompanied by an increase in mortality (Uchino, 2012).
  - One observational cohort study of 134,000 Medicare patients was conducted by the FDA to compare PRADAXA to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within six months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. PRADAXA was found to be associated with a lower risk of ischemic stroke (HR, 0.8; 95% CI, 0.67 to 0.96), ICH (HR, 0.34; 95% CI, 0.26 to 0.46) and death (HR, 0.86; 95% CI, 0.77 to 0.96) vs warfarin. Risk for GI bleeding was higher for PRADAXA (HR, 1.28; 95% CI, 1.14 to 1.44) vs warfarin, and MI risk was similar (HR, 0.92; 95% CI, 0.78 to 1.08). Most results were similar to RE-LY; however, the MI risk was found to be similar between groups rather than an increased risk for PRADAXA as discovered in RE-LY. Also important to note, an increased risk of GI bleeds associated with PRADAXA was similar to the RE-LY study but differs from data found in the Mini Sentinel analysis which found less risk of GI bleeds with new users of PRADAXA vs warfarin (FDA Drug Safety Communication, 2014).
- In NVAF patients who require AF cardioversion, standard oral anticoagulant therapy generally consists of a warfarin-based regimen to prevent thrombosis. More recently, FXa inhibitors have been evaluated for this use. Caution should be exercised when interpreting results of these studies as both were underpowered to demonstrate statistically significant differences for efficacy and safety endpoints. Key results are as follows:
  - The X-VeRT trial randomized 1,504 patients with AF undergoing elective cardioversion to XARELTO dosed between 15 to 20 mg daily depending on renal function or a VKA in a 2:1 ratio. The primary endpoint (defined as a composite of stroke, transient ischemic attack, peripheral embolism, MI, and CV death) occurred in 0.5% of XARETO-treated patients vs 1% of VKA-treated patients. Additionally, the proportion of patients who had major bleeding were similar in the XARELTO and VKA treatment groups (0.6% vs 0.8%, respectively) (Cappato et al, 2014).
  - The ENSURE-AF trial randomized 2,199 NVAF patients undergoing cardioversion to SAVAYSA 30 to 60 mg daily vs an enoxaparin/warfarin regimen. The primary efficacy endpoint (defined as a composite of stroke, systemic embolic event, MI, or CV mortality) occurred in 0.5% of SAVAYSA-treated patients vs 1% of enoxaparin/warfarin-treated patients. Additionally, the proportion of patients who had a first major or clinically relevant non-major bleeding occurrence were similar (1% for each group) (Goette et al, 2016).

Triple anticoagulant therapy after cardiac procedures

- Some patients require triple anticoagulant therapy in cases of cardiac procedures, including PCI, which may be indicated in patients with AF with certain co-morbid diseases. There is limited evidence to guide appropriate treatment. Evidence has been controversial and often outcomes vary greatly according to the population studied requiring clinicians to balance the risk of thrombosis and ischemic stroke with that of potential bleeding. Studies have demonstrated that a $P2Y_{12}$ inhibitor plus aspirin are superior to warfarin in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent, but found oral anticoagulation was superior to dual antiplatelet therapy (DAPT) in reducing the risk of ischemic stroke in patients with AF (Connolly et al, 2006; Cutlip et al, 1999; Gibson et al, 2016; Leon et al, 1998).
  - Prior trials examining the use of oral anticoagulants vs DAPT post-procedurally has yielded mixed results. The ACTIVE-W trial found DAPT was inferior to warfarin for the prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking oral anticoagulation therapy; however, in the STARS trial, DAPT was superior to an oral anticoagulant for the prevention of thrombosis related to coronary stent insertion (Connolly et al, 2006; Cutlip et al, 1999). Most evidence with triple therapy has included warfarin and consists of small open-label (OL) RCTs or observational studies (Dewilde et al, 2013; Fiedler et al, 2015).

  - Recent American Heart Association (AHA) guidance recommends an assessment of CHA2DS2-VASc risk score to estimate the thromboembolic risk and the HASBLED risk score to estimate the hemorrhagic risk. The AHA recommends including the patient in a shared decision regarding the selection of DAPT vs triple therapy as well as the duration of therapy post-procedurally. Although the AHA acknowledges that both European and Canadian guidelines suggest TSOACs over warfarin for triple therapy, this has been based on lower quality observational data and post-hoc analyses (Raval et al, 2017). Current AHA guidance acknowledges that in spite of limited data, certain patients for whom it is difficult to reach and maintain therapeutic INR levels with warfarin may warrant the use of a TSOAC with DAPT (but not in combination with prasugrel or ticagrelor) after PCI (Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017).
- Studies are currently underway examining the benefits and risks of triple anticoagulant therapy. These studies, including the recently published PIONEER-AF-PCI trial and the ongoing RE-DUAL PCI, RT-AF, SAFE-A, and AUGUSTUS studies, will provide further insights into the use of a TSOAC with DAPT in patients undergoing PCI (Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017). A number of studies have been conducted with three of the TSOACs which included triple therapy anticoagulant regimens for the treatment of secondary ACS prevention; however, this indication has not been FDA-approved and the percentage of patients who had concomitant AF has not been well documented:
  - ELIQUIS and PRADAXA have been studied in patients after an ACS via the APPRAISE trials and REDEEM trials, respectively. Trial outcomes resulted in minimal to no clinical benefit; however, an increased risk of harm was observed as bleeding events (Alexander et al, 2009; Cornel et al, 2015; Ogawa et al, 2013; Oldgren et al, 2011).
  - XARELTO has been studied at doses of 2.5 mg or 5 mg twice daily vs placebo in 15,526 patients with recent ACS and followed for approximately two years via the DB, PC, ATLAS trial. ACS patients were also administered DAPT therapy with a low-dose aspirin or thienopyridine (either clopidogrel or ticlopidine). XARELTO 2.5 mg twice daily dosing not only significantly reduced the primary endpoint (defined as the composite of death from CV causes, MI, or stroke; P = 0.02), but unlike the 5 mg dosing, the 2.5 mg dose also reduced the rate of death from CV or any cause (P = 0.002 for both). This benefit, however, was tempered by an increased risk of non-coronary artery bypass grafting (CABG) thrombolysis in myocardial infarction (TIMI) major bleeding (P < 0.001) and ICH (P = 0.04) vs placebo (Mega et al, 2012).
  - The recently conducted PIONEER-AF-PCI trial was a large, OL, randomized safety trial (N = 2,124) conducted in patients with NVAF undergoing PCI with stent placement and compared triple therapy strategies with XARELTO and warfarin. Patients were randomized to: (1) XARELTO 15 mg once daily plus clopidogrel 75 mg daily for 12 months, or (2) XARELTO 2.5 mg twice daily plus DAPT with a prespecified duration of 1, 6 or 12 months, or (3) warfarin plus DAPT with a prespecified duration of 1, 6 or 12 months. Patients administered XARELTO-based regimens had a lower risk of the primary safety endpoint of clinically significant bleeding (composite of major or minor TIMI bleeding or bleeding requiring medical attention) compared to warfarin (17.4% and 26.7%, respectively; P < 0.001). Clinically significant bleeding was driven by bleeding requiring medical attention. For the secondary efficacy endpoints, patients experienced no difference in major adverse CV events (defined as a composite of death from CV causes, MI, or stroke) or stent thrombosis compared to warfarin plus DAPT; however, caution should be exercised as the study was not powered for this outcome and clinical efficacy remains uncertain (Gibson et al, 2015; Gibson et al, 2016).

<u>VTE treatment</u>

- Six large, randomized controlled trials (RE-COVER, RE-COVER II, AMPLIFY, Hokusai-VTE, EINSTEIN-DVT and EINSTEIN-PE) evaluated the efficacy and safety of PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively, for the treatment of acute VTE (although PRADAXA and SAVAYSA trials had 5 to 10 days treatment with a parenteral anticoagulant prior to initiating treatment). Baseline populations for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials varied greatly including the following characteristics (Schulman et al, 2009; Schulman et al, 2009; Agnelli et al [a], 2013; Büller et al, 2013; Bauersachs et al, 2010; Büller et al, 2012; Prins et al, 2013):
  - Patients aged ≥ 75 years ~10%, 14%, 13.5%, and 13 to 17%, respectively
  - Prior VTE ~22%, 16%, 18%, and 19 to 20%, respectively
  - Unprovoked VTE ~ 35%, 89.8%, 65.7%, and 62 to 64.5%, respectively
  - Cancer at baseline ~4.3%, 2.7%, 9.3%, and 5.2%, respectively
  - Duration of treatment: 6 months, 6 months, 3 to 12 months, and measures at 3, 6, and 12 months, respectively

  - TTR ~ 60%, 61%, 64%, and 58 to 63%, respectively
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - For RE-COVER, recurrent VTE and related deaths occurred in 2.4% in the PRADAXA arm and 2.1% in the warfarin arm (P < 0.001 for non-inferiority). Major bleeding was similar (1.6% PRADAXA vs 1.9% warfarin), but more PRADAXA patients discontinued treatment due to adverse events (9%) compared to warfarin (6.8%; P < 0.05) (Schulman et al, 2009).
  - In RE-COVER II, symptomatic VTE or VTE- related deaths occurred in 2.3% of PRADAXA patients vs 2.2% of warfarin patients (P < 0.001 for non-inferiority). Major bleeding was similar; however, warfarin had significantly more overall bleeds in 22.1% of patients compared to 15.6% PRADAXA patients (P < 0.05) (Schulman et al, 2014).
  - In AMPLIFY, non-inferiority was met for the primary outcome of recurrent symptomatic VTE or death related to VTE in 2.3% ELIQUIS patients vs 2.7% conventional therapy patients (RR, 0.84; 95% CI, 0.6 to 1.18). Significantly more major bleeding was observed with conventional therapy (1.8%) compared to patients treated with ELIQUIS (0.6%) (Agnelli et al [a], 2013).
  - For Hokusai-VTE, SAVAYSA was non-inferior to warfarin for the prevention of recurrent VTE after treatment with parenteral anticoagulants (in 3.2% SAVAYSA vs 3.5% warfarin after 12 months follow-up; HR, 0.89; 95% CI, 0.7 to 1.13; P < 0.001 for non-inferiority). Significantly lower rates of major or clinically relevant non-major bleeding were observed in 8.5% of SAYVASA patients compared to 10.3% of warfarin patients (P = 0.004), but major bleeding was similar (P = 0.35) (Büller et al, 2013).
  - The results from EINSTEIN-DVT demonstrated XARELTO to be non-inferior to standard therapy (2.1% for XARELTO vs 3% for enoxaparin/VKA; P < 0.001 for non-inferiority) for symptomatic recurrent VTE. Identical rates (8.1%) of major or non-major clinically relevant bleeding were shown. Net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding favored XARELTO (reported in 2.9% XARELTO vs 4.2% enoxaparin/VKA patients; P = 0.03) (Bauersachs et al, 2010).
  - In EINSTEIN-PE, XARELTO was shown to be non-inferior to enoxaparin/VKA (2.1% XARELTO vs 1.8% enoxaparin/VKA; HR, 1.12; 95% CI, 0.75 to 1.68) for symptomatic recurrent VTE. The principal safety outcome, clinically relevant bleeding, occurred in 10.3% of XARELTO patients and 11.4% of standard therapy patients (HR, 0.9; 95% CI, 0.76 to 1.07; P = 0.23). Major bleeding was observed in 1.1% XARELTO patients and 2.2% in the standard-therapy group (HR, 0.49; 95% CI, 0.31 to 0.79; P = 0.003). Net clinical benefit occurred in 3.4% of XARELTO patients and 4% of standard therapy patients (HR, 0.85; 95% CI, 0.63 to 1.14; P = 0.28) (Büller et al, 2012).

<u>Reduction in Recurrent VTE</u>

- Four large randomized controlled trials (RE-MEDY, RE-SONATE, AMPLIFY-EXT, and EINSTEIN-EXT) were evaluated for the reduction in recurrent VTE and the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, and XARELTO vs placebo, respectively (however, PRADAXA is the only agent compared to warfarin as observed in the RE-MEDY trial). Each trial was an extension of the acute VTE trials mentioned previously. (Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013).
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - The RE-MEDY (comparing PRADAXA to warfarin) and RE-SONATE (comparing PRADAXA to placebo) trials had similar efficacy results with recurrent VTE reported in 1.8% PRADAXA vs 1.3% warfarin (P = 0.01 for non-inferiority) in the RE-MEDY trial and 0.4% PRADAXA vs 5.6% placebo (P < 0.001) in the RE-SONATE trial. However, RE-MEDY displayed lower major bleeding in the PRADAXA group (0.9% PRADAXA vs 1.8% warfarin; HR, 0.52; 95%, 0.27 to 1.02) compared to that of the RE-COVER trials (Schulman et al, 2013).
  - In AMPLIFY-EXT, extended treatment with ELIQUIS demonstrated superiority vs placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause (8.8% placebo vs 1.7% for each ELIQUIS 2.5 and 5 mg groups). Across the trial, the rates of major bleeding were low and comparable (placebo 0.5% vs 0.2% and 0.1% for ELIQUIS 2.5 and 5 mg, respectively) (Agnelli et al [b], 2013).
  - In the EINSTEIN-EXT, XARELTO was superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; P < 0.001). Rates of major bleeding were similar (0.7% vs 0%; P = 0.11). The outcome of net clinical benefit was significantly in favor of XARELTO, with symptomatic recurrent VTE plus major bleeding reported in 2% of XARELTO patients vs 7.1% of placebo patients (P < 0.001) (Bauersachs et al, 2010).

- Current guidelines recommend LMWH in patients who have recurrent VTE, including those currently stable on VKA or TSOAC therapy (Kearon et al, 2016).

VTE prophylaxis for total knee (TKR) and/or hip (THR) replacement surgery

- Nine large randomized, double blinded trials (RE-NOVATE and RE-NOVATE II [hip], RECORD 1 and 2 [hip], RECORD 3 and 4 [knee], ADVANCE 1 and 2 [knee], and ADVANCE 3 [hip]) were the basis for clinical efficacy and safety for PRADAXA, XARELTO, and ELIQUIS vs enoxaparin, respectively in VTE prophylaxis for TKR or THR surgeries. Duration of treatment, dose strength, and frequency varied for each group among trials.
- When evaluating anticoagulation therapies for patients undergoing THR or TKR endpoints use of the surrogate measure, asymptomatic DVT, detected by mandatory venography. The American College of Chest Physicians (ACCP) guidelines find this outcome unsatisfactory due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding. The guidelines provide suggestions to estimate reductions in symptomatic thrombosis; however, this is contingent on available evidence. Many studies rely on asymptomatic DVT events to determine differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates (Guyatt et al, 2012).
- Data from the THR trials found XARELTO and ELIQUIS to be superior to enoxaparin 40 mg once daily and PRADAXA to be non-inferior to enoxaparin 40 mg once daily when prescribed for orthopedic prophylaxis (Eriksson et al, 2008; Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011; Kakkar et al, 2008; Lassen et al, 2010 [a]; Lassen et al, 2010 [b]).
  - RE-NOVATE and RE-NOVATE II: The RE-NOVATE trial compared 150 and 220 mg of dabigatran to enoxaparin 40 mg per day and the RE-NOVATE II trial compared 220 mg of dabigatran to enoxaparin 40 mg per day in over 5,500 patients. In both trials, dabigatran was as effective as enoxaparin in reducing the risk of VTE and mortality after THR surgery (P for non-inferiority < 0.001). The incidence of major bleeding did not differ significantly among groups (enoxaparin 0.9% to 1.6% vs dabigatran 1.3% to 2%) (Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011).
  - ADVANCE-3: Apixaban 2.5 mg twice daily was superior to enoxaparin in approximately 5,400 patients in reducing the risk of VTE and mortality after THR surgery (P < 0.001). The incidence of adjudicated major bleeding events were similar between groups (enoxaparin 0.8% vs apixaban 0.7%) (Lassen et al, 2010 [b]).
  - RECORD 1: Rivaroxaban 10 mg once daily was superior to enoxaparin in approximately 5,600 patients for the combined endpoint of any DVT, nonfatal PE, or all-cause mortality up to day 42 for rivaroxaban and ranged from 1.1% to 2% compared to 3.7% to 9.3% for enoxaparin. Major VTE was decreased 0.2% to 0.6% with rivaroxaban compared with 2% to 5.1% with enoxaparin. The incidence of major bleeding was similar between groups (enoxaparin 0.1% vs rivaroxaban 0.3%; P = 0.18) (Eriksson et al, 2008; Kakkar et al, 2008).
- Studies in patients undergoing a TKR have conflicting results with evidence demonstrating superiority of XARELTO and ELIQUIS when compared to enoxaparin 40 mg dose. However, TKR studies evaluating the US enoxaparin recommended dose of 30 mg twice daily have demonstrated ELIQUIS to be inferior to enoxaparin for total VTE (RR, 1.02; 95% CI, 0.78 to 1.32; P for non-inferiority = 0.06) through the ADVANCE-1 trial (Lassen et al, 2009), and XARELTO has demonstrated superiority to enoxaparin for the primary efficacy endpoint (Turpie et al, 2009).
- It is important to note that guidelines favor LMWH over ARIXTRA, ELIQUIS, PRADAXA, XARELTO, or UFH (AAOS, 2011; Guyatt et al, 2012).

General VTE prophylaxis for the medically ill:

- For patients who are medically ill and at risk for a DVT or PE, two studies (ADOPT and MAGELLAN) have been conducted for ELIQUIS and XARELTO, respectively. Both TSOACs were compared to enoxaparin 40 mg daily for approximately 10 days to ELIQUIS 2.5 mg twice daily for 30 days and XARELTO 10 mg once daily for 35 days, respectively. The following efficacy and safety outcomes were reported in each trial:
  - ADOPT: ELIQUIS was demonstrated to be similar to enoxaparin for the primary endpoint of composite of total VTE and VTE-related death at 30 days (RR, 0.87; 95% CI, 0.62 to 1.23; P = 0.44) and at 90 days (RR, 1.06; 95% CI, 0.69 to 1.63; P = not reported). Enoxaparin treatment was associated with significantly less risk of bleeding compared to ELIQUIS (Goldhaber et al, 2011).
  - MAGELLAN: XARELTO was demonstrated to be as effective as enoxaparin for the primary endpoint of asymptomatic proximal or symptomatic VTE at day 10 (RR, 0.97; 95% CI, 0.71 to 1.31; P = 0.003 for non-inferiority)

and superior to enoxaparin at day 35 (RR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02 for superiority). Enoxaparin treatment was associated with significantly less risk of bleeding compared to XARELTO (Cohen et al, 2013).
  - The clinical relevance of asymptomatic VTE is unknown in the MAGELLAN trial. The ADOPT trial included a number of endpoints, including the composite of VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT, and it is not clear if any of the individual measures were significantly different.

Safety in renal insufficiency:

- One meta-analysis of ten randomized controlled trials examined patients with mild to moderate renal insufficiency and AF, acute DVT/PE, or extended treatment of VTE who were administered recommended doses of TSOACs (e.g., ELIQUIS, PRADAXA, or XARELTO). The analysis of key outcomes demonstrated that TSOACs were non-inferior and had improved bleeding compared to conventional anticoagulant treatment with LMWH, VKA, LMWH followed by VKA, or aspirin therapy (Sardar et al, 2014).

SAFETY SUMMARY

- Contraindications:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
  - COUMADIN, ELIQUIS, JANTOVEN, PRADAXA and XARELTO also have contraindications in patients with a severe hypersensitivity to any component of the products.
  - PRADAXA has an additional contraindication in patients with mechanical prosthetic heart valves.
  - COUMADIN and JANTOVEN are contraindicated in patients with hemorrhagic tendencies or blood dyscrasias, recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces, threatened abortion, eclampsia, preeclampsia, unsupervised patients with conditions associated with potential high level of non-compliance, spinal puncture, other diagnostic or therapeutic procedures with the potential for uncontrollable bleeding, major regional or lumbar block anesthesia, malignant hypertension, or bleeding tendencies associated with active ulceration, overt bleeding of the GI, genitourinary, or respiratory tract, CNS hemorrhage, cerebral aneurysms, dissecting aorta, bacterial endocarditis, pericarditis, or pericardial effusions.
- A boxed warning exists for:
  - PRADAXA, XARELTO, SAVAYSA, and ELIQUIS with regards to the increased risk of thrombotic events when prematurely discontinuing therapy without adequate continuous anticoagulation. Also, treatment with these agents increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis in patients receiving neuraxial anesthesia or undergoing spinal puncture. The optimal timing between the administration of PRADAXA, XARELTO, SAVAYSA, or ELIQUIS and neuraxial procedures is not known.
  - SAVAYSA should not be used in NVAF patients with CrCL > 95 mL/min. In trials, these patients had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin.
  - COUMADIN and JANTOVEN may cause major or fatal bleeding. Drugs, dietary changes, and other factors affect INR levels achieved with COUMADIN or JANTOVEN therapy. Regular monitoring of INR in all patients is recommended.
- Warnings/Precautions:
  - Warnings and precautions for all agents within the oral anticoagulant class include an increased risk of serious or potentially fatal bleeding (including hemorrhage). Patients should be evaluated for signs and symptoms of blood loss or thrombotic events when treated with oral anticoagulants.
  - Additional warnings and precautions for the TSOACs (ELIQUIS, PRADAXA, SAVAYSA, and XARELTO) include a risk of thrombotic events (including stroke) after premature discontinuation, use is not recommended in patients with heart valves (ie, prosthetic, bioprosthetic, mechanical valves, or moderate to severe mitral stenosis), and an increased risk of long-term or permanent paralysis from an epidural or spinal hematoma when neuraxial anesthesia or spinal/epidural puncture is employed in patients treated with an antithrombotic agent.
  - ELIQUIS and XARELTO have a warning and precaution that use is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present with hemodynamic instability or receive thrombolysis or pulmonary embolectomy.
  - COUMADIN, JANTOVEN, and XARELTO has a warning and precaution in pregnant women due to the potential for obstetric hemorrhage. XARELTO may also cause emergent delivery. COUMADIN and JANTOVEN are contraindicated during pregnancy; however, the benefits may outweigh the risks in pregnant patients with mechanical heart valves at high risk of thromboembolism.

- XARELTO has a warning and precaution of use in renal and hepatic impairment.
- An additional warning and precaution for SAVAYSA is reduced efficacy in NVAF patients with CrCL > 95 mL/min.
- COUMADIN and JANTOVEN have a warning and precaution that fatal and serious calciphylaxis or calcium uremic arteriolopathy has been reported with use in patients with and without end stage renal disease. When calciphylaxis is diagnosed, warfarin should be discontinued and an alternate anticoagulant considered. Additional warnings and precautions include the potential for tissue necrosis or gangrene, systemic atheroemboli, cholesterol microemboli, possible limb ischemia, necrosis, and gangrene in patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Should any of these issues occur, COUMADIN or JANTOVEN should be discontinued. Should HIT or HITTS occur, treatment with COUMADIN or JANTOVEN may be considered after the platelet count has normalized.

- Adverse events:
  - The most common adverse reactions reported with these agents include bleeding (all agents), anemia (SAVAYSA), rash (SAVAYSA), abnormal liver function tests (SAVAYSA), and gastritis-like symptoms (PRADAXA).
- Drug interactions:
  - PRADAXA has a warning and precaution of concomitant use with P-gp inducers or inhibitors, and XARELTO has a warning and precaution of combined use with dual P-gp and strong CYP3A4 inhibitors or inducers. Generally use with these products should be avoided. Although not a warning and precaution, interactions between strong P-gp inhibitors or inducers, CYP3A4 inhibitors or inducers, and oral anticoagulants either in combination or when co-administered alone are noted within the ELIQUIS and SAVAYSA labeling.
  - Concomitant use with other drugs (ie, aspirin, platelet inhibitors, antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin reuptake inhibitors [SSRIs], and serotonin norepinephrine reuptake inhibitors [SNRIs]) that impair hemostasis increase the risk of bleeding.
  - Numerous drug and dietary interactions exist for warfarin.
- Additional safety considerations:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
    - Two oral anticoagulants have reversal agents available for urgent situations. These include warfarin (COUMADIN and JANTOVEN) and dabigatran (PRADAXA). Vitamin K functions as a reversal agent for warfarin, and idarucizumab (PRAXBIND) is a specific reversal agent for PRADAXA.
    - A specific reversal agent for ELIQUIS, SAVAYSA, and XARELTO is not available. Hemodialysis does not significantly contribute to clearance. The use of prothrombin complex concentrates (PCC), or other procoagulant reversal agents such as activated prothrombin complex concentrate (APCC) or recombinant FVIIa may be considered but has not been evaluated in studies.
      - Andexanet alfa is a reversal agent under clinical development. On August 17, 2016, a CRL was issued by the FDA questioning manufacturing and clinical data. Portola Pharmaceuticals plan to submit the BLA after deficiencies identified in the CRL have been addressed (Portola Pharmaceuticals press release, 2017).

DOSING AND ADMINISTRATION

- Table 3 outlines general dosing recommendations. Please refer to prescribing information for additional details regarding certain drug interactions, various special populations, converting to other anticoagulants, and guidance as it relates to surgical procedures.

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ELIQUIS (apixaban)	Tablet: 2.5 mg, 5 mg	Reduce the risk of stroke in NVAF: 5 mg twice daily In NVAF patients with at least 2 of the following characteristics: (1) age ≥ 80 years, (2) Body weight ≤ 60 kg, or (3) serum creatinine ≥ 1.5mg/dL, the recommended dose is 2.5 mg twice daily.	--	For patients unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tabs may be crushed and are stable in water, D5W, apple juice or

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Prophylaxis of DVT following hip or knee replacement surgery: Knee: 2.5 mg twice daily for 12 days; Hip: 2.5 mg twice daily for 35 days. Note: First dose should be taken 12 to 24 hrs after surgery. Treatment of DVT and PE: 10 mg twice daily for 7 days, followed by 5 mg twice daily. Reduction in the risk of DVT and PE recurrence: 2.5 mg twice daily after at least 6 months of treatment for DVT or PE.		applesauce. May deliver through a nasogastric tube after mixed in 60 mL of D5W or water.
PRADAXA (dabigatran)	Capsule: 75 mg, 110 mg, 150 mg	Reduce the risk of stroke in NVAF: CrCL > 30 mL/min: 150 mg twice daily; CrCL 15 to 30 mL/min: 75 mg twice daily; CrCL 30 to 50 mL/min with concomitant use of P-gp inhibitors (only dronedarone or ketoconazole): 75 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 30 mL/min. Treatment of DVT and PE/Reduction in the risk of DVT and PE recurrence:* CrCL > 30 mL/min: 150 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min. Prophylaxis of VTE following hip replacement surgery: CrCL > 30 mL/min: 110 mg on the first day, then 220 mg once daily for 28 to 35 days; Note: The initial dose should be taken 1 to 4 hrs after surgery. Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min.	--	Take with or without food.
SAVAYSA (edoxaban)	Capsule: 15 mg, 30 mg, 60 mg	Reduce the risk of stroke in NVAF: CrCL 95 to 51 mL/min: 60 mg once daily; for CrCL 15 to 50 mL/min: 30 mg once daily; Do not use for CrCL > 95 mL/min Treatment of DVT and PE: 60 mg once daily following 5 to 10 days of initial parenteral anticoagulant; CrCL 15 to 50 mL/min, weight ≤ 60 kg, or taking concomitant P-gp inhibitors: 30 mg once daily	--	Take with or without food.
XARELTO (rivaroxaban)	Tablet: 10 mg, 15 mg, 20 mg	Prophylaxis of DVT following hip or knee replacement surgery: Knee: 10 mg once daily for 12 days Hip: 10 mg once daily for 35 days Note: The initial dose should be taken 6 to 10	--	The 10 mg, 15 mg and 20 mg tablets may be crushed and are stable in water or

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Starter pack (tablet): 15 and 20 mg	hrs after surgery. Reduce the risk of stroke in NVAF: CrCL > 50 mL/min: 20 mg once daily with the evening meal CrCL 15 to 50 mL/min: 15 mg once daily with the evening meal Treatment of DVT and PE: 15 mg twice daily with food, for first 21 days. Then after 21 days, 20 mg once daily with food for remaining treatment Reduction in the risk of recurrence of DVT and of PE: 20 mg once daily with food		applesauce for up to 4 hours.
COUMADIN; JANTOVEN (warfarin)	Tablet: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg	Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 for most bioprosthetic and mechanical heart valves and an INR of 2.5 to 3.5 for tilting disk valves, bileaflet mechanical valves in the mitral position, or caged ball or caged disk valves Prophylaxis and treatment of venous thrombosis and its extension, PE: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 and treat for a minimum of 3 months and reassess the risk-benefit ratio of long-term treatment. Reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI: Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; for high risk patients with MI, maintain an INR of 2 to 3 (moderate intensity) plus low-dose aspirin ≤ 100 mg/day for at least 3 months after MI	An INR > 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding Dosing may be modified in patients with certain identified genotypes.	

Abbreviations: AF = atrial fibrillation; CrCL = creatinine clearance; CYP450 = cytochrome P450; DVT = deep vein thrombosis; MI = myocardial infarction; NVAF = non-valvular atrial fibrillation; PE = pulmonary embolism; P-gP = P-glycoprotein
*For treatment of DVT/PE, PRADAXA is recommended after 5 to 10 days of parenteral anticoagulation. For reduction in the risk of recurrence of DVT/PE, PRADAXA is recommended after previous treatment.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ELIQUIS (apixaban)	In trials, a range of 32 to > 69% were ≥ 65 years of age, and 13 to > 31% were ≥ 75 years of age. No clinically significant differences in efficacy and safety have been observed in older patients.	Safety and efficacy have not been established.	Doses of 2.5 mg twice daily are recommended in NVAF patients with two of three criteria: (1) age ≥ 80 years; (2) body weight ≤ 60 kg; (3) sCr ≥ 1.5 mg/dL. ESRD has not been studied.	No dose adjustment in mild impairment, dosing recommendations cannot be provided for moderate impairment, and use is not recommended in severe impairment.	Pregnancy Category B Unknown whether excreted in breast milk; A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
PRADAXA (dabigatran)	In trials, a total of 85% were ≥ 65 years of age, and 40% were ≥ 75 years of age. Risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable.	Safety and efficacy have not been established.	No dose adjustment in mild to moderate impairment. Doses of 75 mg twice daily are recommended in NVAF patients with: (1) CrCL 15 to 30 mL/min or (2) CrCL 30 to 50 mL/min plus co-administration with a P-gp inhibitor.	--	Pregnancy Category C Unknown whether excreted in breast milk; A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
SAVAYSA† (edoxaban)	In trials, a range of 32 to 74% were ≥ 65 years of age, and 14 to 41% were ≥ 75 years of age. No clinically significant differences in efficacy and safety have been observed in older patients.	Safety and efficacy have not been established.	Lower doses to 30 mg once daily for CrCL 15 to 50 mL/min. Use is not recommended for CrCL < 15 mL/min.	No dose adjustment is needed in mild impairment. Use is not recommended in moderate to severe impairment.	Pregnancy Category C Unknown whether excreted in breast milk; A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
XARELTO (rivaroxaban)	In trials, a range of 37 to 77% were ≥ 65 years of age, and 15 to 38%	Safety and efficacy have not been established.	Lower doses to 15 mg once daily in NVAF with CrCL 15 to 50	Avoid use in moderate to severe impairment or with any	Pregnancy Category C Unknown whether excreted in breast milk; A decision should

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	were ≥ 75 years of age. Risk of thrombotic events and bleeding increases with age, but the risk-benefit profile is favorable.		mL/min. Use is not recom-mended for CrCL < 30 mL/min for the treatment, prophylaxis, or risk reduction of DVT and/or PE. ESRD has not been studied.	coagulopathy-associated hepatic disease.	be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
COUMADIN/ JANTOVEN (warfarin)	Patients aged > 60 years have a greater than expected INR response. Consider lower initiation and maintenance doses in elderly patients.	Safety and efficacy data is limited to patient registries and observational studies. When taking warfarin, patients should avoid any activity or sport that may result in traumatic injury. More frequent INR values are recommended in pediatric patients. Infants and children receiving vitamin K nutrition, such as formulas, may be warfarin-resistant.	No dose adjustment in impairment. Renal clearance is a minor determinant.	Impairment could potentiate the drug response. Use with caution in these patients.	Contraindicated in pregnancy, except in women with mechanical heart valves. Exposure in the first trimester resulted in approximately 5% of congenital malformations. Based on published data (N = 15), warfarin was not detected in human milk; however, human milk-fed infants may be sensitive to warfarin therapy. Caution is advised; monitor breast fed infants for bruises or bleeds.

Abbreviations: CrCL = creatinine clearance; DVT = deep vein thrombosis; ESRD = end stage renal disease; NVAF = non-valvular atrial fibrillation; PE = pulmonary embolism; sCr = serum creatinine; TCR = therapeutic class review

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

†In patients with a body weight of ≤ 60 kg, reduce the SAVAYSA dose to 30 mg.

(Clinical Pharmacology, 2017)

CONCLUSION

- The four TSOACs, PRADAXA, XARLETO, SAVAYSA, and ELIQUIS, are all indicated for the reduction of stroke and systemic embolism in NVAF and for the treatment of DVT and PE, otherwise known as events caused by a VTE. PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE; and DVT and PE prophylaxis in patients undergoing THR. XARELTO and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing TKR surgery. Warfarin has various indications, including prophylaxis and/or treatment of PE; prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement prophylaxis and/or treatment of venous thrombosis and its extension; and to reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI.
- Warfarin has long-term efficacy and safety data and is generically available. Trial evidence and recommendations from current clinical guidelines support the use of warfarin for all FDA-approved indications.
- Therapy with warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- The major advancement with the TSOACs is that they do not require routine laboratory monitoring; however, this may make it difficult for physicians to objectively assess adherence to therapy. In addition, their propensity for drug and dietary interactions is less than warfarin. There is uncertainty regarding how to manage bleeding or perioperative management in patients treated with TSOACs. There are no FDA-approved assays or calibration reagents to measure the effect of the TSOACs. However, partial thromboplastin time (PTT) and thrombin time (TT) can be useful for measuring the effects of PRADAXA (Raval et al, 2017).
- PRADAXA is the first TSOAC with an available antidote, idarucizumab (PRAXBIND prescribing information, 2015). There are no specific antidotes for ELIQUIS, SAVAYSA, or XARELTO; however, antidotes, ciraparantag and andexanet alfa, are in the pipeline (Perosphere press release, 2016; Portola Pharmaceuticals press release, 2017).
- Warfarin, SAVAYSA, and XARELTO are approved for once-daily dosing, while ELIQUIS is administered twice-daily. Based on the indication, PRADAXA may be administered once or twice-daily. PRADAXA, ELIQUIS, SAVAYSA, and XARELTO require a dose adjustment in patients with renal impairment and are only available as branded products.
- No head-to-head studies have been conducted comparing the TSOACs. Also, there is a lack of long-term efficacy and safety data and limited real-world experience with the TSOACs.
- In terms of current available evidence, the following has been demonstrated:
  - For the prevention of stroke and systemic embolism in patients with NVAF, all TSOACs have been found to be superior or non-inferior to warfarin within pivotal trials; however, clinical differences have not been clearly defined (Connolly et al, 2009; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011). Guidelines generally recommend oral anticoagulation in patients with NVAF at intermediate to high risk of stroke, or in certain patients with ≥ 1 moderate risk factors for stroke or thrombosis. TSOACs are considered to be a reasonable option in patients with native aortic valve disease, tricuspid valve disease, or mitral regurgitation, and in AF with a CHA_2DS_2-VASc score ≥ 2. Warfarin is generally recommended over the TSOACs, particularly for prosthetic or bioprosthetic valve thrombosis. Expert consensus guidelines stipulate that continuous uninterrupted VKA therapy has demonstrated lower bleeding risks vs interrupted treatment with heparin bridging for certain procedures such as pacemaker implants or implantable cardioverter defibrillators (ICD) in most NVAF patients. Reputable societies encourage decisions to be made based on patient characteristics and a risk/benefit analysis (Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017).
  - All TSOACs have demonstrated non-inferiority to conventional therapy for acute VTE. XARELTO (EINSTEIN-PE only) and ELIQUIS have also demonstrated significant reductions in major bleeds; however, PRADAXA and SAVAYSA have similar rates of major bleeding compared to that observed with conventional therapy. Due to the design of the trials, SAVAYSA and PRADAXA also require 5 to 10 days of parenteral anticoagulation prior to initiating treatment (Agnelli et al [a], 2013; Bauersachs et al, 2010; Büller et al, 2013; Büller et al, 2012; Prins et al, 2013; Schulman et al, 2009; Schulman et al, 2014). The ACCP guidelines recommend the TSOACs over warfarin for the first 3 months of therapy for non-cancer associated VTE. Warfarin is recommended over LMWH for long-term VTE therapy; however LMWH is preferred in patients with cancer (Guyatt et al, 2012; Kearon et al, 2016).

- For the reduction of risk recurrence of VTE as demonstrated in extended VTE trials, PRADAXA, ELIQUIS, and XARELTO have demonstrated superiority to placebo for recurrent VTE; however, bleeding rates were comparable. PRADAXA has demonstrated non-inferiority to warfarin with less risk of major or clinically relevant bleeding and had lower major bleeding rates than those rates observed in the RE-COVER trials (Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013). For patients with recurrent VTE and currently administered anticoagulants, the ACCP guidelines recommend patients be switched to LMWH, at least temporarily, in lieu of warfarin and TSOACs. If a recurrent VTE occurs while a patient is taking long-term LMWH, then a dose increase of 1/4 or 1/3 is recommended (Guyatt et al, 2012; Kearon et al, 2016).
- For VTE prophylaxis in patients undergoing TKR or THR surgery, XARELTO has demonstrated superiority to enoxaparin doses in both THR and TKR studies. ELIQUIS was found to be superior for THR and when compared to enoxaparin 40 mg once daily for TKR; however, ELIQUIS was found to be inferior to the US enoxaparin recommended dose of 30 mg twice daily (Eriksson et al, 2008; Kakkar et al, 2008; Lassen et al, 2009; Lassen et al, 2010 [b]; Turpie et al, 2009). The FDA has approved PRADAXA for VTE prophylaxis associated with THR surgery after non-inferiority was demonstrated compared to enoxaparin 40 mg once daily and bleeding rates were similar (Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011). The AAOS does not recommend a specific medication (AAOS, 2011). The ACCP does favor LMWH over ARIXTRA, ELIQUIS, XARELTO, or UFH (Guyatt et al, 2012). If a TSOAC is prescribed, the treatment duration of ELIQUIS and XARELTO is a minimum of 10 to 14 days for a TKR (prescribing information recommends 12 days) and 35 days for a THR which is in agreement with the prescribing information.

REFERENCES

- Agnelli G, Büller HR, Cohen A, et al [a]. Oral apixaban for the treatment of acute venous thromboembolism (AMPLIFY). N Engl J Med. 2013 Aug 29;369(9):799-808.
- Agnelli G, Büller HR, Cohen A, et al [b]. Apixaban for extended treatment of venous thromboembolism (AMPLIFY-EXT). N Engl J Med. 2013 Feb 21;368(8):699-708.
- Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic stroke. Cochrane Database of Systematic Reviews. 2005, Issue 3. Art. No.:CD001927. DOI:10.1002/14651858.CD001927.pub2.
- Alexander JH, Becker RC, Bhatt DL, et al; for the APPRAISE Steering Committee. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009;119(22):2877-85.
- American Academy of Orthopaedic Surgeons. AAOS Clinical Practice Guideline: Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty. J Am Acad Orthop Surg. 2011 Dec;19(12):777-8.
- Anderson JL, Halperin JL, Albert NM, et al. Management of Patients With Atrial Fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations): A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. April 1, 2013. Circulation. 2013;127:1916-26.
- Benjamin E, Blaha MJ, Chiuve, SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report from the American Heart Association. Circulation. 2017;135(10):e146-603.
- Bauersachs R, Berkowitz ST, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510.
- Büller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97.
- Büller HR, Décousus H, Grosso MA, et al; for the Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct 10;369(15):1406-15.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45(5):1545-88. doi: 10.1161/01.str.0000442009.06663.48
- Bytzer P, Connolly SJ, Yang S, et al. Analysis of upper gastrointestinal adverse events among patients given dabigatran in the RE-LY trial. Clin Gastroenterol Hepatol. 2013 Mar;11(3):246-52.e1-5.
- Cannon CP, Gropper S, Bhatt DL, et al. Design and Rationale of the RE-DUAL PCI Trial: A Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy With Dabigatran Etexilate Versus Warfarin Triple Therapy in Patients With Nonvalvular Atrial Fibrillation Who Have Undergone Percutaneous Coronary Intervention With Stenting (RE-DUAL PCI). Clin Cardiol. 2016 Oct;39(10):555-564. doi: 10.1002/clc.22572
- Cappato R, Ezekowitz MD, Klein AL, et al; for the X-VeRT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014 Dec 14;35(47):3346-55.
- Centers for Disease Control and Prevention (CDC). Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) – Blood Clot Forming in a Vein. Last updated March 1, 2017. Available at: https://www.cdc.gov/ncbddd/dvt/index.html. Accessed March 14, 2017.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology.com. Accessed March 10, 2017.
- Cohen AT, Spiro TE, Büller HR, et al. Extended duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. J Thromb Thrombolysis. 2011; 31: 407–16.
- Cohen D, Rivaroxaban: can we trust the evidence? BMJ. 2016;352:i575.

- Connolly SJ, Pogue J, Hart R, et al; for the ACTIVE Writing Group of the ACTIVE investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903-12.
- Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806-17.
- Connolly SJ, Wallentin L, Ezekowitz MD, et al. The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. Circulation. 14 June 2013:128:237-43.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran vs warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
- Connolly SJ, Wallentin L, Yusuf S, et al. Additional events in the RE-LY trial. N Engl J Med. 2014 Oct 9;371:1464-65. DOI: 10.1056/NEJMc1407908.
- Cornel JH, Lopes RD, James S, et al; for the APPRAISE-2 Study Group. Anticoagulant therapy and outcomes in patients with prior or acute heart failure and acute coronary syndromes: Insights from the APixaban for PRevention of Acute ISchemic Events 2 trial. Am Heart J. 2015;169(4):531-8.
- COUMADIN prescribing information. Bristol-Myers Squibb Company. Princeton, New Jersey. September 2016.
- Culebras A, Messe SR, Chaturvedi S, et al. Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. Feb 25, 2014;82(8):716-24.
- Cundiff DK, Manyemba J, Pezzullo JC. Anticoagulants vs non-steroidal anti-inflammatories or placebo for treatment of venous thromboembolism. Cochrane Database of Systematic Reviews. 2006, Issue 1. Art. No.:CD003746. DOI:10.1002/14651858. CD003746.pub2.
- Cutlip DE, Leon MB, Ho KK, et al. Acute and nine-month clinical outcomes after "suboptimal" coronary stenting: results from the STent Anti-thrombotic Regimen Study (STARS) registry. J Am Coll Cardiol.1999;34(3):698-706.
- Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial (WOEST). Lancet. 2013;381:1107-15.
- Drugs@FDA. Food and Drug Administration. 2017. Available at: http://www.accessdata.fda.gov. Accessed March 7, 2017.
- ELIQUIS prescribing information. Bristol-Myers Squibb Company. Princeton, New Jersey. July 2016.
- Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-75.
- Eriksson BI, Dahl OE, Rosencher N, et al [a]. RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial (RE-NOVATE). Lancet. 2007;370:949-56.
- Eriksson BI, Dahl OE, Rosencher N, et al [b]. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial (RE-NOVATE). [correction]. Lancet. 2007;370(9604):2004.
- Eriksson BI, Dahl OE, Huo MH, et al. RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomized, double-blind, noninferiority trial. Thromb Haemost. 2011;105:721Y729.
- Eriksson BI, Dahl OE, Rosencher N, et al [c]; for the RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5:2178Y2185.
- European Medicines Agency (EMA) press release. EMA concludes defective device in ROCKET study does not impact Xarelto's safety. May 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002465.jsp&mid=WC0b01ac058004d5c1. Accessed March 16, 2017.
- FDA Risk Evaluation and Mitigation Strategies (REMS). Approved Risk Evaluation and Mitigation Strategies (REMS). 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed March 14, 2017.
- FDA drug safety communication. FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin. May 13, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Accessed March 14, 2017.
- FDA press release. FDA analyses conclude that Xarelto clinical trial results were not affected by faulty monitoring device. October 11, 2016. Available at: https://www.fda.gov/drugs/drugsafety/ucm524678.htm. Accessed March 10, 2017.
- Fiedler KA, Maeng M, Mehilli J, et al. Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation (ISARTRIPLE). J Am Coll Cardiol. 2015;65(16):1619-29.
- Furie KL, Goldstein LB, Albers GW, et al. Oral Antithrombotic Agents for the prevention of stroke in nonvalvular atrial fibrillation: A Science Advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:3442-3453.
- Gao F, Shen H, Wang ZJ, et al. Rationale and design of the RT-AF study: combination of rivaroxaban and ticagrelor in patients with atrial fibrillation and coronary artery disease undergoing percutaneous coronary intervention (RT-AF). Contemp Clin Trials. 2015;43:129–132. doi: 10.1016/j.cct.2015.05.012.
- Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (PIONEER AF-PCI). N Engl J Med. Dec 2016;375(25):2423-34.
- Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin k antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J. 2015;169(4):472-8.
- Giugliano RP, Ruff CT, Braunwald E, et al; for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093-104.
- Giugliano RP, Ruff CT, Rost NS, et al. Cerebrovascular events in 21,105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke. 2014 Aug;45(8):2372-8.
- Goette A, Merino JL, Ezekowitz MD, et al; for the ENSURE-AF Investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet. 2016;388(10055):1995-2003.
- Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med.. 2011;365:2167-2177.
- Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
- Guyatt GH, Akl EA, Crowther M, et al. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(Suppl 2):7-47.

- Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (randomized evaluation of long-term anticoagulation therapy) trial. Circulation. 2012;125:669-76.
- Hoshi T, Sato A, Nogami A, et al; for the SAFE-A Investigators. Rationale and design of the SAFE-A study: SAFety and Effectiveness trial of apixaban use in association with dual antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention (SAFE-A). J Cardiol. 2017 Apr;69(4):648-651. doi: 10.1016/j.jjcc.2016.06.007.
- Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2006, Issue 1. Art. No.:CD0001367. DOI:10.1002/14651858.CD001367.pub2.
- JANTOVEN prescribing information. Upsher-Smith Laboratories, Inc. Minneapolis, MN. October 2011.
- January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267.
- Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban vs short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial. Lancet. 2008 Jul 5;372(9632):31-9.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):293-294.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 May;45:2160-2236.
- Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin for thromboprophylaxis after knee replacement (ADVANCE 1). N Engl J Med.. 2009;361:594-604.
- Lassen MR, Raskob GE, Gallus A, et al [a]. ADVANCE-2 Investigators. Apixaban versus enoxaparin for the thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. Lancet. 2010;375:807-15.
- Lassen MR, Gallus A, Raskob GE, et al [b]. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement (ADVANCE 3). N Engl J Med.. 2010a;363:2487-2498.
- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339:1665-71.
- Lopes RD, Crowley MJ, Shah BR, et al. Stroke Prevention in Atrial Fibrillation. AHRQ Comparative Effectiveness Reviews. Rockville, MD. Agency for Healthcare Research and Quality; Aug 2013. Report Number: 13-EHC113-EF.
- Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomized, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015;385:2280-87.
- Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome (ATLAS ACS 2-TIMI 51). N Engl J Med. 2012;366(1):9-19.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com. Accessed March 14, 2017.
- Middeldorp S, Prins MH, Hutten BA. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database Syst Rev. 2014 Aug 5;8:CD001367. doi: 10.1002/14651858. CD001367.pub3.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. [Epub ahead of print]. Circulation. 2017 Mar 15. pii: CIR.0000000000000503. doi: 10.1161/CIR.0000000000000503.
- Ogawa H, Goto S, Matsuzaki M, et al; for the APPRAISE-J Committee. Randomized, double-blind trial to evaluate the safety of apixaban with antiplatelet therapy after acute coronary syndrome in Japanese patients. Circ J. 2013;77(9):2341-8.
- Oldgren J, Budaj A, Granger C, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial (REDEEM). European Heart Journal. 2011;32:2781-9.
- Orange Book: Approved Drug Products and Therapeutic Equivalence Evaluations. 2016. Available at: http://www.accessdata.fda.gov. Accessed March 14, 2017.
- Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults with Aortic Stenosis. J Am Coll Cardiol. 2017 Mar 14;69(10):1313-46.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban vs warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.
- Perosphere press release. Ciraparantag (PER977): Broad-Spectrum Anticoagulant Reversal Agent. 2016. Available at: http://perosphere.com/content/research/per977.htm. Accessed March 14, 2017.
- Portola Pharmaceuticals press release. Andexanet alfa: FXa Inhibitor Antidote. 2017. Available at: https://www.portola.com/clinical-development/andexanet-alfa-fxa-inhibitor-antidote/. Accessed March 15, 2017
- PRADAXA prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. November 2015.
- PRAXBIND prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. October 2015.
- Prins MH, Lensing AW, Bauersachs R, et al; for the EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J. 2013;11(1):21.
- Raval AN, Cigarroa JE, Chung MK, et al. Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association. [Epub ahead of print]. Circulation. 2017 Mar 7; 135(10):e604-33. doi: 10.1161/CIR.0000000000000477.
- Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors vs vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. Cochrane Database of Systematic Reviews. 2010, Issue 4. Art. No.:CD005981. DOI:10.1002/14651858.CD005981.pub2.
- SAVAYSA prescribing information. Daiichi Sankyo, Inc. Parsippany, NJ. September 2016.
- Sardar P, Chatterjee S, Herzog E, et al. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Canadian J of Cardiol. 2014;30:888-97.
- Saxena R, Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic stroke. Cochrane Database of Systematic Reviews. 2004, Issue 2. Art. No.:CD000185. DOI:10.1002/14651858.CD000185.pub2.

- Schulman S, Kearon C, Kakkar AK, et al. RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361:2342Y2352.
- Schulman S, Kakkar AK, Goldhaber SZ, et al. RE-COVER II Study Group. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014 Feb 18;129(7):764-72.
- Schulman S, Kearon C, Kakkar AK, et al. RE-MEDY and RE-SONATE Study Group. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368:709-18.
- Smith EE, Saposnik G, Biessels GJ, et al. Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2017 Feb;48(2):e44-71.
- Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban vs enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. Lancet. 2009 May 16;373(9676):1673-80.
- Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012 Mar 12;172(5):397-402.
- van der Heijden JF, Hutten BA, Büller HR, et al. Vitamin K antagonists or low-molecular-weight heparin for the long term management of symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews. 2001, Issue 3. Art. No.:CD002001. DOI:10.1002/14651858.CD002001.
- XARELTO prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. October 2016.

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Therapeutic Class Overview
Platelet Aggregation Inhibitors

INTRODUCTION

- Cardiovascular (CV) disease was the cause of 30.8% of all deaths, or approximately 1 of every 3 in the United States (US) in 2014 according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2017 update. Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after CV disease, cancer, chronic lower respiratory disease, and unintentional injuries/accidents, in which more women die (58% of all US stroke deaths) from stroke every year than men (Benjamin et al, 2017).
- Platelet inhibitors play a major role in the management of CV, cerebrovascular, and peripheral vascular diseases. These agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes (ACS) (myocardial infarction [MI], unstable angina [UA]), stroke/transient ischemic attack (TIA), intermittent claudication, prevention of postoperative thromboembolic complications, thrombocythemia, and valvular heart disease. The use of these agents as both monotherapy or combination therapy by national and international clinical guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events (Amsterdam et al, 2014; Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Fihn et al, 2012; Gerhard-Herman et al, 2016; Guyatt et al, 2012; January et al, 2014; Jauch, 2013; Kernan et al, 2014; Lansberg et al, 2012; Levine et al, 2011; Levine et al, 2016a; Levine et al, 2016b; Meschia et al, 2014; Nishimura, 2017; O'Gara et al, 2013; Powers et al, 2015; Roffi et al, 2016; Smith et al, 2011; Smith et al, 2017; Vandvick et al, 2012).
- The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action and have characteristics that distinguish agents from one another.
    - Aspirin, a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A2, a platelet aggregant and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that aspirin reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease (Harrington et al, 2008).
        - Omeprazole, a component of YOSPRALA (aspirin delayed-release [DR]/omeprazole), in combination with aspirin, is an antisecretory compound which suppresses gastric acid secretion by inhibiting the $[H^+/K^+]$-ATPase enzyme system of the gastric parietal cells. Omeprazole has been characterized as a gastric acid-pump inhibitor as it blocks the final step of gastric acid production, and inhibits both basal and stimulus-induced acid secretion.
    - Vorapaxar is a newer agent and unique to the class as a selective antagonist of the protease-activated receptor-1 (PAR-1), a primary thrombin receptor, and should only be used with aspirin and/or clopidogrel according to their indication or standards of care.
    - Clopidogrel, prasugrel, ticagrelor, and ticlopidine inhibit $P2Y_{12}$, an adenosine phosphate receptor on the surface of platelets. Ticagrelor is the only reversible inhibitor of $P2Y_{12}$ and unlike clopidogrel does not require hepatic activation. Clopidogrel has a slower onset of action, incomplete platelet inhibition, and poor response in certain patients including those with CYP2C19 polymorphisms. Ticlopidine can cause severe neutropenia. Compared to clopidogrel, the benefits of prasugrel have been seen as early as 3 days. Prasugrel and vorapaxar are both contraindicated in patients with a history of TIAs.
    - Anagrelide has multiple mechanisms in which it exerts its action and is unique in class as it has the ability to reduce platelet counts without affecting white or red blood cell counts.
    - Cilostazol reversibly inhibits platelet aggregation through cyclic AMP phosphodiesterase inhibition. Cilostazol also has vasodilating activity which has benefits in treating certain diseases.
    - Dipyridamole is a non-nitrate coronary vasodilator that also inhibits platelet aggregation. The mechanism of action of dipyridamole may involve its ability to vasodilate and to increase concentrations of adenosine, a platelet aggregation inhibitor.

- Products included in this class review include anagrelide, aspirin/extended-release (ER) dipyridamole, BRILINTA® (ticagrelor), cilostazol, clopidogrel, dipyridamole, DURLAZA™ (aspirin extended release [ER]), EFFIENT® (prasugrel), ticlopidine, YOSPRALA™ (aspirin DR/omeprazole), and ZONTIVITY™ (vorapaxar). Other platelet aggregation inhibitors used only in inpatient acute care settings, such as the glycoprotein IIb/IIIa inhibitors and KENGREAL™ (cangrelor) are not discussed in this review.
  - Medispan Class: Platelet Aggregation Inhibitors – Platelet Aggregation Inhibitors, Platelet Aggregation Inhibitors Combinations, Phosphodiesterase III Inhibitors, Direct-Acting $P2Y_{12}$ Inhibitors, Quinazoline Agents, Thienopyridine Derivatives, and Cyclopentyltriazolopyrimidine (CPTP) Derivatives.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Single-Entity Agents			
AGRYLIN® (anagrelide)	Various	03/14/1997	✔
DURLAZA (aspirin ER)	New Haven	09/04/2015	-
PLAVIX® (clopidogrel)	Various	11/17/1997	✔
PLETAL® (cilostazol)	Various	01/15/1999	✔ *
PERSANTINE® (dipyridamole)	Various	12/06/1961	✔ *
EFFIENT (prasugrel)	Eli Lilly	07/10/2009	-†
BRILINTA (ticagrelor)	AstraZeneca	07/20/2011	-
TICLID® (ticlopidine)	Various	10/31/1991	✔ *
ZONTIVITY(vorapaxar)	Merck & Co	05/08/2014	-
Combination Products			
AGGRENOX (aspirin/ER dipyridamole)	Various	11/22/1999	✔
YOSPRALA™ (aspirin DR/omeprazole)	Aralez	09/14/2016	-

* Brand no longer available.
† The earliest a generic will launch is anticipated is 2023 due to pediatric exclusivity.
(DRUGS@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Drug
Treatment of patients with thrombocythemia, secondary to myeloproliferative neoplasms, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events	anagrelide*
Reduce the risk of death and MI in patients with chronic coronary artery disease (CAD), such as patients with a history of MI or unstable angina pectoris or with chronic stable angina, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA	DURLAZA (aspirin ER)†
Reduction of symptoms of intermittent claudication, as demonstrated by an increased walking distance	cilostazol
Recent MI, recent stroke, or established peripheral arterial disease (PAD)	clopidogrel‡
Reduce the rate of thrombotic CV events in patients with ACS	clopidogrel‡§
Prevention of postoperative thromboembolic complications of cardiac valve replacement	dipyridamole‖
Reduce the rate of thrombotic CV events in patients with ACS who are being managed with percutaneous coronary intervention (PCI)	EFFIENT (prasugrel)¶
Reduce the rate of CV death, MI, and stroke in patients with ACS or a history of MI. Also reduces the rate of stent thrombosis in patients who have been stented for the treatment of ACS	BRILINTA (ticagrelor) #
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation	ticlopidine**
Reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	ticlopidine††
Reduce thrombotic CV events in patients with a history of MI or with PAD	ZONTIVITY (vorapaxar)‡‡
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	aspirin/ER dipyridamole
Aspirin component: Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, reducing the combined risk of death and nonfatal MI in patients with previous MI or unstable angina pectoris, reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, and for patients who have undergone coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) when there is a pre-existing condition for which aspirin is already indicated. Omeprazole component: Decrease the risk of developing aspirin-associated gastric ulcers in at-risk patients due to age (≥55 years) or documented history of gastric ulcers.	YOSPRALA (aspirin DR/omeprazole)†§§

* Approved in adult and pediatric patients (studied in patients aged ≥7 years).
† Not indicated for use in situations where a rapid onset of action is required (such as acute treatment of MI or before PCI).
‡ Clopidogrel has been shown to reduce the rate of MI and stroke.
§ For patients with non-ST-elevation ACS (UA/non-ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction (STEMI). Clopidogrel should be administered in conjunction with aspirin.
‖ As an adjunct to coumarin anticoagulants.
¶ Patients who are to be managed with PCI as follows: patients with UA or NSTEMI and patients with STEMI when managed with primary or delayed PCI.
# Administer with a daily maintenance dose of aspirin of 75 to 100 mg. For at least the first 12 months following ACS, it is superior to clopidogrel.
** As adjunctive therapy with aspirin.
†† Due to the potential for life-threatening blood dyscrasias (eg, thrombotic thrombocytopenic purpura [TTP], neutropenia/agranulocytosis, and aplastic anemia), ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.
‡‡ Has only been studied as an addition to aspirin and/or clopidogrel. There is limited experience with other antiplatelet drugs or with ZONTIVITY as monotherapy.
§§ Has not been shown to reduce the risk of gastrointestinal (GI) bleeding due to aspirin.

Prescribing information: AGGRENOX, 2015; AGRYLIN, 2015; BRILINTA, 2016; DURLAZA, 2015; EFFIENT, 2016; PERSANTINE, 2011; PLAVIX, 2016; PLETAL, 2016; ticlopidine, 2016; YOSPRALA, 2016; ZONTIVITY, 2015)

Information on indications, mechanism of action, pharmacokinetics, and safety information has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Antiplatelet therapy plays an important role in the long-term prevention of stroke or TIAs. In a large, meta-analysis of patients with a previous MI, acute MI, previous TIA/stroke, and acute stroke, as well as patients with an increased risk of atherothrombotic events, it was demonstrated that overall, antiplatelet therapy reduced the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 25%. With regard to individual endpoints, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25% and vascular death by 15% (Antithrombotic Trialists' Collaboration, 2002).
- There are few head-to-head studies comparing the various antiplatelets. In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review of antiplatelet and anticoagulant treatments. The study authors concluded that prasugrel reduced rates of CV death, MI or stroke at 30 days in patients undergoing early invasive treatments when compared to clopidogrel and in UA/NSTEMI patients after 1 year, as did clopidogrel and ticagrelor (Melloni et al, 2013). Another systematic review of large, quality trials observing dual antiplatelet therapy (DAPT) of clopidogrel, prasugrel, or ticagrelor plus aspirin when compared to aspirin monotherapy found DAPT with prasugrel or ticagrelor and aspirin vs DAPT with clopidogrel and aspirin was not associated with a risk reduction of stroke. The authors also noted conflicting results within trials (Gouya et al, 2014). A double-blind, randomized controlled trial compared the efficacy of ticagrelor vs clopidogrel to lower the risk of CV death, MI, or ischemic stroke in 13,885 patients with symptomatic PAD, with a median follow-up of 30 months. The primary efficacy end point occurred in 10.8% of patients receiving ticagrelor vs 10.6% receiving clopidogrel (hazard ratio [HR] 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65). Major bleeding occurred at the same frequency with both treatments (1.6%), and ticagrelor was discontinued more often than clopidogrel, mainly due to dyspnea (4.8% vs 0.8% (Hiatt et al, 2017). A 6-month, open-label, randomized trial of 181 Chinese patients with poor/intermediate metabolizer phenotypes of CYP2C19 with ACS undergoing PCI, demonstrated that ticagrelor significantly reduced the composite risk of death, stroke, or recurrent MI vs high-dose clopidogrel (4.4% vs 20%, P<0.001) There were no significant differences in major bleeding events between groups, but dyspnea (16.5%) was more common with ticagrelor treatment (Zhang et al, 2016).
- For individual platelet inhibitors, data from clinical studies demonstrated that ticlopidine reduced the risk of stroke and other vascular outcomes in patients with cerebrovascular disease (Gent et al, 1989; Hass et al, 1989). The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic PAD who were treated with clopidogrel experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with aspirin (relative risk reduction [RRR], 8.7% in favor of clopidogrel; 95% CI, 0.3 to 16.3; P=0.043) (Antithrombotic Trialists' Collaboration, 2002; CAPRIE, 1996). Results from the MATCH study demonstrated that the addition of aspirin to clopidogrel in high-risk patients with a recent ischemic stroke or TIA was associated with a nonsignificant difference in reducing major vascular events. In this trial, DAPT was associated with more life-threatening, major, and minor bleeds (Diener et al, 2004). In the ESPRIT study, patients within 6 months of a TIA or minor stroke of presumed arterial origin were randomized to receive aspirin with or without dipyridamole. The rate of the primary composite outcome, death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (whichever occurred first), was 13% with combination therapy vs 16% with aspirin (HR, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction, 1% per year; 95% CI, 0.1 to 1.8) (ESPRIT Study Group, 2006).
- With regard to the treatment of ACS, in the CLARITY-TIMI 28 study, patients who presented within 12 hours of a STEMI were randomized to receive either clopidogrel or placebo for 30 days. Treatment with clopidogrel was associated with a reduction of the composite endpoint of occluded infarct-related artery on angiography, death, or recurrent MI before angiography (Sabatine et al, 2005a). Patients included in the COMMIT study were admitted within 24 hours of a suspected acute MI and received either combination therapy with clopidogrel and aspirin or aspirin monotherapy. In this study, there was a significant reduction in the risk of the composite endpoint of death, re-infarction, or stroke (P=0.002), and in death from any cause (P=0.03) in patients receiving combination therapy after 15 days (COMMIT, 2005). In the CURE study investigators compared long-term (3 to 12 months) combination therapy with clopidogrel plus aspirin to aspirin monotherapy in patients with a NSTEMI who presented within 24 hours of symptom onset. The results demonstrated that combination therapy resulted in a 20% RRR in the composite outcome of nonfatal MI, stroke, or vascular death (P<0.001). The compelling benefit of combination therapy noted in the CURE study was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the study, the associated reduction was not significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not significant (CURE, 2001; Harrington et al, 2008; Lansberg et al, 2012). Meta-analyses of ACS patients or those undergoing PCI to reduce thrombotic events, have conflicting results. Results reported clopidogrel was superior to placebo in reducing the risk of CV death and stroke. Prasugrel or ticagrelor treatment when compared to clopidogrel provided additional benefit regarding CV mortality and MI, but no advantage in stroke (Aradi et al, 2013). A secondary analysis of the TRILOGY ACS trial found intensive antiplatelet

therapy with prasugrel may be beneficial in reducing CV deaths, MIs, or strokes when an angiography is performed prior to treatment and anatomic coronary disease is confirmed (Roe et al, 2012; Wiviott et al, 2013). The CHARISMA study was another long-term trial (median, 28 months) that enrolled and randomized patients with clinically evident CV disease to either combination treatment with clopidogrel and aspirin or to monotherapy with aspirin. The rate of the primary composite endpoint of MI, stroke, or death from CV causes was not different between the 2 treatments (6.8 vs 7.3%; relative risk, 0.93; 95% CI, 0.83 to 1.05; P=0.22) (Bhatt et al, 2006). There is also limited evidence that clopidogrel has a greater impact on preventing the composite of CV death, MI, and stroke in smokers compared to non-smokers (Gagne et al, 2013). A meta-analysis evaluated the clinical efficacy and safety of $P2Y_{12}$ inhibitors in patients with STEMI undergoing primary PCI, as defined by composite major adverse CV events (MACE). At one month, the analysis suggested that prasugrel was associated with lower MACE vs clopidogrel (standard dose odds ratio [OR] 0.59; 95% CI, 0.50 to 0.69) and ticagrelor (standard dose OR 0.69; 95% CI, 0.56 to 0.84); lower mortality and MI vs clopidogrel and standard ticagrelor; and lower stroke risk vs standard clopidogrel and ticagrelor. At one year, prasugrel was associated with lower mortality and MACE vs clopidogrel and ticagrelor. In general, prasugrel and ticagrelor were more efficacious vs clopidogrel (Rafique et al, 2016).

- The duration of DAPT has been highly debated and often controversial. Evolving evidence has consistently demonstrated that estimated benefits are accompanied by a certain proportion of risk; therefore, not all patients would benefit from DAPT treatment. To further complicate interpretations, often first-generation stents were studied for DAPT; however, newer stents have improved safety benefits, but studies and analyses often have ≥ 1 methodological limitations reducing publication strengths. Current evidence includes an analysis of the National Heart, Lung, and Blood Institute (NHLBI) observational registry which followed over 3,000 ACS patients following PCI with a drug-eluting stent (DES) found that patients who continued on DAPT (clopidogrel plus aspirin) were associated with lower mortality after 1 year, but had a higher risk of repeat PCI within 4 years (Mulukutala et al, 2013). The PRODIGY trial demonstrated that clopidogrel plus aspirin administered in patients who received a DES or bare metal stent for 24 months was not significantly more effective than a 6 month clopidogrel regimen in reducing the composite of death due to any cause, MI, or cerebrovascular accident (Valgimigli et al, 2012). However, the DAPT trial found patients who continued DAPT beyond 1 year after the placement of a DES compared with aspirin therapy alone, significantly reduced the risk of stent thrombosis, major adverse CV and cerebrovascular events, including MI; but was associated with an increased risk of bleeding and all-cause mortality (Mauri et al, 2014). Several meta-analyses/systemic reviews have concluded there is no increased risk of stent thrombosis with shorter duration DAPT, and treatment is associated with a lower risk of bleeding. Meta-analyses restricted to predominantly newer generation DES have demonstrated increased trends of increased all-cause mortality associated with prolonged durations of DAPT (Elmariah et al, 2015; Navarese et al, 2015; Udell et al, 2016). A recent meta-analysis determined that long-term DAPT was associated with a significant decrease in risk of death, MI, and stroke, primarily in patients with prior MI or stroke, but not PAD, while long-term DAPT was also associated with increased major bleeding. Of note, the study was not able to evaluate the impact of DES on atherothrombotic events (Fanari et al, 2017). Another meta-analysis assessed the efficacy and safety of duration of DAPT in patients with implantation of predominantly newer-generation DES. The analysis determined treatment with DAPT for 12 months vs 3 to 6 months resulted in no significant differences in incidences of death, major hemorrhage, or MI. DAPT for 18 to 48 months vs 6 to 12 months was also associated with no difference in incidence of all-cause death, but showed decreased MI and stent thrombosis, and increased major hemorrhage. A risk-benefit analysis found 3 fewer stent thromboses and 6 fewer MIs but 5 more major bleeds per 1,000 patients/year treated with prolonged DAPT. Also, treatment with DAPT >1 year after MI reduced the composite risk of CV death, MI, or stroke but increased major bleeding (Bittl et al, 2016).
- A meta-analysis of 16 randomized controlled trials looking at the effects of antiplatelet agents (e.g., aspirin, aspirin plus dipyridamole, and aspirin plus clopidogrel) and vitamin K antagonists for the prevention of thrombosis in patients with lower limb atherosclerosis undergoing bypass grafting found therapy with aspirin or aspirin plus dipyridamole had an effect on peripheral bypass grafts and prosthetic graft patency, but not venous grafts alone. Treatment with clopidogrel plus aspirin had greater increases of bleeding, but no difference in primary graft patency compared to aspirin alone (Bedenis et al, 2015).
- The major clinical study demonstrating the safety and efficacy of ticagrelor for its FDA-approved indication is the PLATO study. PLATO was an international, double-blind, double-dummy, multicenter, randomized-controlled trial that compared ticagrelor to clopidogrel in adult patients hospitalized with documented ACS, with or without ST-segment elevation within the previous 24 hours (N=18,624). After 12 months, the risk of the primary composite endpoint of vascular death, MI, or stroke was significantly reduced with ticagrelor (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; P<0.001). Ticagrelor also significantly reduced the risk of the secondary endpoints of the composite of all-cause mortality, MI, or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001); the composite of vascular death,

MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event (14.6 vs 16.7%; HR, 0.88; 95% CI, 0.81 to 0.95; P<0.001); MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; P=0.005), and vascular death (4 vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91). Furthermore, ticagrelor significantly reduced the risk of all-cause mortality (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89). Rates of major bleeding were not different between the 2 treatments (P=0.43) (Wallentin et al, 2009).

- Several subanalyses of the PLATO study have been conducted (James et al, 2011; Cannon et al, 2010; Steg et al, 2010; James et al, 2010a; James et al, 2010b; Held et al, 2011; Wallentin et al, 2010; Mahaffey et al, 2011; Storey et al, 2011; Becker et al, 2011; Banerjee et al, 2008; Kohli et al, 2013; Husted et al, 2014; Varenhorst et al, 2014; Velders et al, 2016). One subanalysis found ticagrelor was associated with fewer first and recurrent composite CV events based on the entire international study population (Kohli et al, 2013). In patients with ACS undergoing noninvasive (P=0.045) or invasive procedures (P=0.0025), ticagrelor remained more efficacious compared to clopidogrel (James et al, 2011; Cannon et al, 2010). However, in patients with ST-elevation or left bundle branch block (P=0.07), chronic kidney disease (P=0.13), or diabetes (P value not reported), and in those who underwent coronary artery bypass graft surgery (P=0.29), there was no difference between ticagrelor and clopidogrel with regard to the primary composite endpoint (Steg et al, 2010, James et al, 2010a; James et al, 2010b; Held et al, 2011). In patients with or without ST-elevated ACS, gender was not a risk factor for outcomes, but some signals alluded to men benefiting most. The number of primary events that occurred in men was double that of women (Husted et al, 2014). A genetic substudy was also conducted and demonstrated ticagrelor to be more efficacious than clopidogrel, irrespective of cytochrome P450 2C19 and ABCB1 polymorphisms (P=0.0380) (Wallentin et al, 2010). In the original PLATO study, a significantly higher rate of dyspnea was observed with ticagrelor; however, data from a substudy revealed ticagrelor had no effect on pulmonary function (Wallentin et al, 2009; Storey et al, 2011). In terms of causes of death, ticagrelor appeared to have a greater effect on sudden death over clopidogrel within the study population (Varenhorst et al, 2014). Another post-hoc subgroup analysis of patients with STEMI treated with primary PCI demonstrated treatment with ticagrelor resulted in a reduction of the primary end point compared with clopidogrel (7.9% versus 8.6%; P=0.38) (Velders et al, 2016).
- Mahaffey et al compared the effects of ticagrelor and clopidogrel among patients enrolled in the PLATO study who were from the United States (N=1,413). The superior benefits of ticagrelor in reducing thrombotic CV events were not observed among this specific patient population. Specifically, there was no difference between ticagrelor and clopidogrel in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 7.75; P=0.1459). The authors discussed that among these patients who were treated with ticagrelor, the lowest event rates were observed in patients also receiving low-dose aspirin maintenance therapy. In contrast, event rates in those treated with clopidogrel were similar regardless of concurrent high- or low-dose aspirin. Despite the potential role that aspirin maintenance dosing may play in explaining the regional differences observed within the PLATO study, the authors noted that the pattern of results are consistent with what might be expected by chance alone in a large, multiregional clinical study with multiple exploratory analyses. A potential mechanism by which high-dose aspirin is thought to reduce the effects of ticagrelor relates to its ability to inhibit the endothelial release of prostacyclin in a dose-dependent fashion at doses greater than 80 mg/day. Prostacyclin reduces platelet reactivity and may contribute synergistically *in vivo* to the antiplatelet effects of $P2Y_{12}$ inhibitors. Therefore, the therapeutic effects of a higher mean level of $P2Y_{12}$ inhibition achieved with ticagrelor in the PLATO study may be attenuated when endogenous prostacyclin production is inhibited (Mahaffey et al, 2011). Until a prospective clinical study comparing the effects of low- vs high-dose aspirin maintenance therapy and its effect on the efficacy of ticagrelor is conducted, it remains unclear as to why the diminished effects of ticagrelor in the United States population were observed. Of note, the FDA-approved dosing of ticagrelor recommends that after the initial loading dose of aspirin (325 mg), a daily maintenance dose of aspirin of 75 to 100 mg should be used.

- The FDA approval of ticagrelor for the reduction in the rate of CV death, MI, and stroke in patients with a history of MI was based on results from the PEGASUS TIMI-54 trial. Approximately 21,000 patients who had a MI at least 1 to 3 years prior and had a high risk factor for another event were randomized to treatment with ticagrelor 90 mg twice daily, 60 mg twice daily, or placebo in addition to aspirin 75 to 150 mg and followed for a median time of 33 months. The primary composite endpoint of time to first event of CV death, MI, or stroke was significantly reduced by 16% with ticagrelor 60 mg twice daily plus aspirin with event rates 1.27% lower at 3 years in the ticagrelor 60 mg twice daily plus aspirin group compared to those patients treated with aspirin alone (P=0.004) (Bonaca et al, 2015). Subgroup analyses have also demonstrated similar outcomes for the primary endpoint of MACE between patients with and without diabetes (Bhatt et al, 2016).The primary safety endpoint, TIMI major bleeding, was significantly increased with

ticagrelor treatment but to a lesser degree with the 60 mg twice daily dose (ticagrelor 60 mg twice daily plus aspirin, 2.3% vs aspirin monotherapy, 1.1%; P<0.001) (Bonaca et al, 2015). The rates of CV mortality or all-cause mortality alone were not significantly different from aspirin monotherapy.

- The SOCRATES trial evaluated approximately 13,200 patients with an acute, non-severe ischemic stroke or high-risk TIA who had not received intravenous or intra-arterial thrombolysis, were not considered to have had a cardioembolic stroke, and were treated with either ticagrelor or aspirin for 90 days. Ticagrelor was not significantly superior to aspirin in reducing stroke, MI, or death at 90 days, the primary endpoint (6.7% of the ticagrelor group vs 7.5% of those treated with aspirin; P=0.07). Additionally, no secondary endpoints were considered significantly different between treatment groups but generally trended towards favoring ticagrelor (with the exception of death and CV death). Exploratory analyses indicated that ticagrelor may be more effective at 7 days in reducing ischemic stroke and all stroke. However, more patients discontinued treatment in the ticagrelor group (17.5%) vs the aspirin group (14.7%), mainly due to dyspnea and any bleeding (Johnston et al, 2016).
    - A subgroup analysis of SOCRATES assessed patients from Asian countries (N=3,858), as the composite of stroke, MI, or death occurred at an increased rate in patients from Asia compared with patients outside of Asia (10.6% vs 5.7%, nominal P<0.01), with higher incidence of major or minor bleeding events in patients from Asia (2.1% vs 1.2%, respectively). In the patients from Asia, treatment with ticagrelor significantly reduced the rate of the composite endpoint compared with aspirin treatment (9.6% vs 11.6%; HR, 0.81; 95% CI, 0.67 to 0.99), with no significant differences in the rates of major bleeding between treatment groups (Wang et al, 2017).
- The major clinical trial demonstrating the safety and efficacy of prasugrel for its FDA-approved indication was the TRITON-TIMI 38 (N=13,608). Results demonstrated that prasugrel was significantly more effective than clopidogrel in reducing ischemic events in patients with ACS who underwent PCI. However, the trial did not demonstrate a decrease in the mortality rate with prasugrel. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with prasugrel. Of note, certain patient subgroups, specifically those who were ≥75 years of age, those weighing <60 kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with prasugrel (Wiviott et al, 2007). In addition, several subgroup analyses were also conducted based on TRITON-TIMI 38 and 1 patient subgroup in particular, those with diabetes, were found to have a significantly greater reduction in ischemic events with prasugrel when compared to nondiabetic patients being treated with either prasugrel or clopidogrel (Antman et al, 2008; Montalescot et al, 2009; Murphy et al, 2008; O'Donoghue et al, 2009; Pride et al, 2009; Wiviott et al, 2008a; Wiviott et al, 2008b).
    - As concluded in the TRILOGY ACS study, in patients with UA/NSTEMI who do not undergo revascularization, when added to aspirin therapy, prasugrel did not significantly reduce the frequency of death from CV causes, MI, or stroke, as compared with DAPT with clopidogrel and aspirin, and similar risks of bleeding were observed (Kohli et al, 2014; Roe et al, 2012). However, a secondary analysis of patients who underwent angiography prior to prasugrel treatment experienced fewer CV deaths, MIs, or strokes than those who were in the clopidogrel arm (Roe et al, 2012; Wiviott et al, 2013).
- First-in-class PAR-1 antagonist, vorapaxar, was FDA-approved based on a post-hoc analysis of patients with a history of MI or PAD who were taking aspirin and/or a thienopyridine (mainly clopidogrel) concomitantly. A safety review terminated the full TRACER trial and patients with stroke in the TRA 2°P-TIMI 50 trial due to significantly increased risks for bleeding, including intracranial hemorrhage (ICH). Both trials were placebo-controlled. In the TRA 2°P-TIMI 50 trial, vorapaxar demonstrated effectiveness in the secondary prevention of CV events, mainly MI and the composite endpoint of CV death, MI, or stroke, primarily driven by the reduction in MI. Although TRA 2°P-TIMI 50 was not designed to evaluate the benefits and risks of vorapaxar in individual patient subgroups, an analysis of patients who were comprised of post-MI and PAD without a history of stroke or TIA was evaluated by the FDA for approval. Those results showed three-year Kaplan Meier (K-M) event rate for the primary efficacy endpoint of 7.9% in the vorapaxar group compared to 9.5% in the placebo group (HR, 0.8; 95% CI, 0.73 to 0.89; P<0.001). The benefit of vorapaxar is tempered by the significant increase of bleeding with vorapaxar use compared to placebo. Significantly increased bleeding rates were also observed in the TRA 2°P-TIMI 50 trial for GUSTO moderate or severe bleeding, TIMI clinically significant bleeding, and GI bleeding (NNH=97, 25, 98, respectively). However, there was no significant difference between placebo and ZONTIVITY for fatal bleeds (Morrow et al, 2012; Tricoci et al, 2012; FDA Summary Review [ZONTIVITY], 2014; FDA Advisory Committee Transcript [ZONTIVITY], 2014). Subgroup analyses have concluded that increased bleeding risks may not be observed in all populations. A pre-specified subgroup analysis of stable patients with a history of previous MI determined that vorapaxar reduced the primary endpoint, whether treated concomitantly with a thienopyridine or not, and the risks of GUSTO moderate or severe bleeding were similarly increased irrespective of thienopyridine use (P-interaction=0.37) (Bohula et al, 2015). Other subgroup analyses have

been published and include a number of the TRA 2°P–TIMI 50 primary study authors. These subgroup analyses found a significant difference in the composite primary endpoint of CV death, MI, or stroke for patients with a prior MI but no statistically significant difference in PAD patients; treatment with vorapaxar in patients with a prior MI was also associated with greater reductions in CV death, MI, or stroke in patients with ≥ 1 risk factors for recurrent events, with greatest risk reductions in patients with ≥ 3 risk factors (Bohula et al, 2016; Bonaca et al, 2012; Scirica et al, 2013). However, the quality of the sub-group analyses is not superior to that of the primary study and the validity of the results is uncertain as methodological limitations were noted. A recent meta-analysis of five randomized controlled trials (N=40,630) demonstrated treatment with vorapaxar vs placebo resulted in a statistically non-significant reduction in risk of MI (risk reduction [RR] 0.86; 95% CI 0.80 to 0.93, P=0.427) and ischemic stroke (RR 0.84; 95% CI 0.72 to 0.97, P=0.920), with no observed differences in all-cause mortality or TIMI bleeding (Sharma et al, 2017).

- The FDA approval of YOSPRALA (aspirin DR/omeprazole) was based on 2 identically-designed, 6-month, phase 3, multi-center, double-blind, active-control, randomized controlled trials conducted in the US. The trials compared aspirin DR/omeprazole 325/40 mg (n=524) against enteric-coated (EC) aspirin 325 mg (n=525), each administered orally once daily for secondary CV disease prevention in patients who had been taking aspirin 325 mg daily for ≥3 months and who were at risk for aspirin-associated gastric ulcers. Patients taking non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) at baseline were allowed to continue therapy if use was chronic and expected to continue throughout the study period. The primary endpoint was the cumulative incidence of endoscopically-determined gastric ulceration over 6 months. Aspirin DR/omeprazole significantly reduced the cumulative incidence of gastric ulcers vs EC aspirin 325 mg in the pooled analysis (3.2% vs 8.6%, respectively; P<0.001). Among NSAID-users at baseline, the cumulative incidence of endoscopic gastric ulcer at month 6 was 4.5% with aspirin DR/omeprazole vs 10.2% in the EC aspirin group, while rates among patients not taking NSAIDs were 3.1% with aspirin DR/omeprazole vs 8.4% in the EC aspirin group. Significantly fewer patients treated with aspirin DR/omeprazole) discontinued therapy due to pre-specified upper GI AEs vs patients treated with EC aspirin arm (1.5% vs 8.2%, respectively; P<0.001) (Whellan et al, 2014).
    - The long-term CV and GI safety of aspirin DR/omeprazole were evaluated in a 12-month, phase 3, multi-center, open-label, single-arm trial among patients who were taking aspirin 325 mg daily for ≥3 months for secondary CVD prevention and were at risk for aspirin-associated upper GI events (N=379). After 12 months, no new or unexpected safety events were noted with aspirin DR/omeprazole, while the most common treatment-emergent GI AEs were diarrhea, dyspepsia, and nausea (each occurred in 4 to 5% of the overall safety population). Gastroesophageal reflux disease (GERD) was reported in 1.8% of the overall population (Goldstein et al, 2016).
- DURLAZA (aspirin ER) 162.5 mg was the first aspirin ER formulation approved by the FDA to reduce the risk of death and MI in patients with chronic CAD, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA. New efficacy studies were not submitted to the FDA for the approval of aspirin ER. While aspirin ER 162.5 mg has a similar pharmacodynamic effect as immediate-release aspirin 81 mg, the clinical benefits of the ER formulation vs immediate-release formulations of aspirin are not yet known (DRUGS@FDA.com, 2017).
- There is no evidence to support the use of dipyridamole in the acute treatment of patients presenting with a non-ST-segment elevation ACS (Harrington, 2008). In addition, the results of a large meta-analysis of 29 randomized-controlled studies demonstrated that in patients with arterial vascular disease, dipyridamole had no clear effect on the secondary prevention of vascular death. Compared to control (no drug or another antiplatelet inhibitor), dipyridamole appeared to reduce the risk of vascular events; however, the effect was only significant in patients presenting with cerebral ischemia (De Schryver et al, 2007).
- In patients with stable intermittent claudication, cilostazol therapy has been shown to provide improvement in walking distance and speed as determined by standardized exercise treadmill tests and functional status questionnaires (Beebe et al, 1999; Bedenis et al, 2014; Money et al, 1998; Reilly, 2001). Results of several randomized, double-blind, placebo-controlled studies of 6 to 24 weeks' duration indicate that cilostazol is more effective than placebo in increasing initial (until onset of claudication pain) and absolute (intolerable pain) claudication distances (Bedenis et al, 2014; Beebe et al, 1999; Money et al, 1998; O'Donnell et al, 2009a; O'Donnell et al, 2009b; Reilly, 2001). Limited data suggest that cilostazol (100 mg twice daily) also may be more effective than pentoxifylline (400 mg 3 times daily) in improving walking distance in patients with intermittent claudication (Bedenis et al, 2014; Beebe et al, 1999; Dawson et al, 2000; Hiatt, 2001; Reilly, 2001).
    - Because of its antiplatelet activity, cilostazol has been used alone or in combination with other antiplatelet agents (e.g., aspirin, clopidogrel) to prevent thrombosis and restenosis following coronary angioplasty/stent implantation (Douglas et al, 2005; Guyatt et al, 2012; Kunishima et al, 1997; Park et al, 1999; Park et al, 2000; Schömig et al, 2005; Take et al, 1997; Tsuchikane et al, 1999; Xu et al, 2016; Yoon et al, 1999; Zou et

al, 2015). In a randomized, double-blind, placebo-controlled study, patients undergoing coronary artery stent implantation with bare-metal stents who received cilostazol (100 mg twice daily for 6 months) in addition to therapy with aspirin and clopidogrel (75 mg daily for 30 days) had a larger minimal coronary artery lumen diameter (primary end point) and a 36% reduction in the risk of restenosis (defined as narrowing of the stented coronary artery lumen by at least 50% as documented by quantitative coronary angiography) (Douglas et al, 2005; Schömig et al, 2005). However, more recent studies, including a recent randomized controlled trial and a systematic review of 10 randomized controlled trials, comparing triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) with DAPT (aspirin and clopidogrel), failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes (e.g., reinfarction, major bleeding, mortality, periprocedural MI) when added to clopidogrel and aspirin therapy (Guyatt et al, 2012; Xu et al, 2016). For patients undergoing DES implantation in coronary arteries, a meta-analysis of 7 randomized controlled trials evaluated the long-term efficacy and safety of adding cilostazol to conventional DAPT (aspirin and clopidogrel). The analysis demonstrated that the addition of cilostazol was associated with a significant reduction in MACE vs DAPT (relative risk 0.66; 95% CI, 0.50 to 0.88), without increasing bleeding, but was associated with significantly higher rates of rash, GI adverse effects, headache, and drug discontinuation (Zou et al, 2015).

- Anagrelide is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (Anagrelide study group, 1992; Birgegard et al, 2004; Dombi et al, 2017; Harrison et al, 2005; Penninga et al, 2004; Silver, 2005; Steurer et al, 2004; Wiviott et al, 2007).

SAFETY SUMMARY

- Boxed warnings associated with antiplatelet treatment include significant, sometimes fatal, bleeding with BRILINTA, EFFIENT, and ZONTIVITY treatment. Additionally, EFFIENT should not be prescribed in patients ≥75 years of age, body weight <60 kg, those with a propensity to bleed, and with concomitant use of medications that increase the risk of bleeding. BRILINTA should not be used with aspirin in doses >100 mg due to reduced effectiveness. The effectiveness of clopidogrel is dependent on the activation of CYP2C19; therefore, there is a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (termed “CYP2C19 poor metabolizers”). The use of another platelet $P2Y_{12}$ inhibitor should be considered in patients identified as CYP2C19 poor metabolizers. Additionally, clopidogrel has a warning and precaution for diminished antiplatelet activity with concomitant use of drugs that interfere with CYP2C19 (e.g., omeprazole, esomeprazole). Concomitant use with omeprazole or esomeprazole and clopidogrel should be avoided. Cilostazol is contraindicated in patients with heart failure of any severity. Ticlopidine has a boxed warning of life-threatening hematological adverse reactions when used in the presence of certain hematopoietic disorders.
- Clopidogrel, EFFIENT, BRILINTA, ZONTIVITY, and ticlopidine are contraindicated in patients with active pathological bleeding such as bleeding peptic ulcer or ICH, and active pathologic bleeding is cited as a warning and precaution within the cilostazol labeling. Withholding ZONTIVITY for a brief period will not be useful in managing an acute bleeding event because of its long half-life. There is no known treatment to reverse the antiplatelet effect of ZONTIVITY, and significant inhibition of platelet aggregation remains four weeks after discontinuation. Because of the short half-life of clopidogrel’s active metabolite, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
- EFFIENT and ZONTIVITY are also contraindicated in patients with a history of prior TIA or stroke, and in ZONTIVITY patients with a history of ICH. Ticlopidine and clopidogrel are contraindicated in severe hepatic impairment. Aspirin/ER dipyridamole, DURLAZA (aspirin ER), and YOSPRALA (aspirin DR/omeprazole) are contraindicated in patients with a known allergy to NSAIDs, in patients with asthma, rhinitis, and nasal polyps, or in children or adolescents with viral infections due to the risk of Reye’s syndrome. Other contraindications are included within boxed warnings.
- Anagrelide has no contraindications.
- Clopidogrel, BRILINTA, EFFIENT, and ticlopidine should be discontinued prior to surgery. Thrombotic thrombocytopenic purpura (TTP) may occur after brief exposure (<2 weeks) of clopidogrel, BRILINTA, or EFFIENT. Premature discontinuation of clopidogrel, BRILINTA, or EFFIENT may increase the risk of CV events. Dyspnea has been reported in patients administered BRILINTA; continuation with BRILINTA without interruption or another antiplatelet should be considered. BRILINTA and ticlopidine have not been studied in patients with severe hepatic or renal impairment. Hypersensitivity reactions, including rash and angioedema, have been reported with clopidogrel and EFFIENT use in patients with a history of prior thienopyridine hypersensitivity. Ticlopidine has been associated with

increased cholesterol within one month of therapy and has not been studied concomitantly with heparin, oral anticoagulants, or fibrinolytic agents.

- Aspirin/ER dipyridamole, DURLAZA (aspirin ER), and YOSPRALA (aspirin DR/omeprazole) should be used with caution in patients at increased bleeding risk such as patients with GI ulcers, a history of active peptic ulcer disease, and/or concomitant alcohol (≥3 drinks daily). Agents containing aspirin may cause fetal harm, especially during the third trimester. Aspirin and anagrelide should not be co-administered as use increases the risk of bleeding.
- Concomitant use of YOSPRALA (aspirin DR/omeprazole) with clopidogrel should be avoided, as omeprazole reduces the pharmacologic activity of clopidogrel. Omeprazole has also been associated with acute interstitial nephritis, *Clostridium difficile*-associated diarrhea, increased risk of bone fracture, cutaneous and systemic lupus erythematosus, hypomagnesemia, and vitamin B-12 deficiency.
- Anagrelide may cause vasodilation, tachycardia, palpitations, and congestive heart failure (CHF). Other drugs that inhibit PDE-3 have caused decreased survival when compared with placebo in patients with CHF (class III to IV). Because of the positive inotropic effects and side effects of anagrelide, a pre-treatment CV examination is recommended in addition to careful monitoring during treatment. Anagrelide increased QT prolongation in healthy volunteers; therefore, anagrelide should not be used in patients with known risk factors for QT prolongation. In addition, interstitial lung diseases, mostly as progressive dyspnea with lung infiltrations, have been reported to be associated with the use of anagrelide in postmarketing reports.
- Cilostazol may induce tachycardia, palpitation, tachyarrhythmia or hypotension, with an associated increase in heart rate of approximately 5 to 7 bpm. Increased risks of exacerbations of angina pectoris or MI may occur in patients with a history of ischemic heart disease. Cilostazol has not been studied in patients with hemostatic disorders or active bleeding and should be avoided in these groups. Patients should be monitored periodically for complete blood count (CBC) abnormalities. Cilostazol has not been studied in patients with moderate or severe hepatic impairment.
- Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe CAD or in patients with hypotension. Chest pain may be aggravated in patients with underlying CAD who are receiving dipyridamole. Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Anagrelide	Capsule: 0.5 mg, 1 mg	Thrombocythemia, secondary to myeloproliferative disorders: Pediatric - Initial, 0.5 mg once daily; Adult - Initial, 0.5 mg 4 times daily or 1 mg twice daily for ≥1 week; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count <600,000/µL (most doses range from 1.5 to 3 mg/day); maximum, 10 mg/day or 2.5 mg in a single dose	Increase dose by no more than 0.5 mg/day in any 1 week	
DURLAZA (aspirin ER)	Capsule: 162.5 mg	Patients with chronic CAD: 162.5 mg once daily Patients who have had an ischemic stroke or TIA: 162.5 mg once daily		Do not take 2 hours before or 1 hour after consuming alcohol

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Cilostazol	Tablets: 50 mg, 100 mg	Intermittent Claudication: 100 mg twice daily	Reduce dose to 50 mg twice daily with concomitant CYP3A4 or CYP2C19 inhibitors	Take at least half an hour before or 2 hours after breakfast and dinner. If symptoms are not improved after 3 months, discontinue treatment.
Clopidogrel	Tablet: 75 mg, 300 mg	ACS: Initial, 300 mg as a single loading dose; maintenance, 75 mg once daily† Recent MI, stroke or established PAD: 75 mg once daily without a loading dose		
Dipyridamole	Tablet: 25 mg, 50 mg, 75 mg	Prevention of postoperative thromboembolic complications of cardiac valve replacement: 75 to 100 mg 4 times daily‡		
EFFIENT (prasugrel)	Tablet: 5 mg, 10 mg	ACS who are being managed with PCI: Initial, 60 mg as a single loading dose (risk of bleeding was increased with early administration [loading dose]§ in patients undergoing PCI or early CABG); maintenance, 5 to 10 mg once daily‖	Consider 5 mg once daily for patients <60kg. Patients should also take aspirin (75 mg to 325 mg) daily.	Take with or without food
BRILINTA (ticagrelor)	Tablet: 60 mg, 90 mg	ACS or a history of MI: Initial, 180 mg (2 tablets) as a single loading dose; maintenance, 90 mg twice daily for the first year and then after 1 year 60 mg twice daily¶		Take with or without food. May be crushed, mixed with water, or administered via nasogastric tube. Do not administer with another oral $P2Y_{12}$ platelet inhibitor. In healthy patients, platelet transfusion did not reverse the effects of BRILINTA and is not likely beneficial for bleeding incidences.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ticlopidine	Tablet: 250 mg	Patients undergoing successful coronary stent implantation: 250 mg twice daily for up to 30 days# Patients who have had a completed thrombotic stroke: 250 mg twice daily		Take with food.
ZONTIVITY* (vorapaxar)	Tablet: 2.08 mg (equivalent to 2.5 mg vorapaxar sulfate)	A history of MI or with PAD: Take 1 (2.08 mg) tablet orally once daily	Use with aspirin and/or clopidogrel according to their indications or standard of care. There is limited experience with other antiplatelets and none with ZONTIVITY as the only antiplatelet agent.	Take with or without food.
Aspirin/ ER dipyridamole	Capsule: 25/200 mg	Patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis: 25/200 mg twice daily	In case of intolerable headaches during initial treatment, switch to 1 capsule at bedtime and low-dose aspirin in the morning; resume twice daily dosing within 1 week.	Take with or without food. Do not chew capsule
YOSPRALA (aspirin DR/ omeprazole)	Tablet: 81/40 mg 325/40 mg	Secondary prevention of CV and cerebrovascular events: 81/40 mg once daily	81 mg has been accepted as an effective dose for secondary CV prevention; providers should consider need for 325 mg and refer to current clinical practice guidelines	Take at least 60 minutes before a meal

*There is limited clinical experience with other antiplatelet drugs or with ZONTIVITY as a monotherapy agent. Also due to the risk of bleeding, ZONTIVITY should be avoided in patients taking warfarin or other anticoagulants. Withholding ZONTIVITY for a brief period will not be useful in managing acute bleeding events because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of ZONTIVITY therapy also remain poorly defined.
† Initiating clopidogrel without a loading dose will delay establishment of an antiplatelet effect by several days.
‡ As adjunct to the usual warfarin therapy. Aspirin is not to be administered concomitantly with coumarin anticoagulants.
§ In the clinical trial, the loading dose of EFFIENT was not administered until coronary anatomy was established in UA/NSTEMI patients and in STEMI patients presenting >12 hours after symptom onset. In STEMI patients presenting within 12 hours of symptom onset, the loading dose was administered at the time of diagnosis, although most received EFFIENT at the time of PCI. For the small fraction of patients that required urgent CABG after treatment with EFFIENT, the risk of significant bleeding was substantial.
‖ The safety and efficacy of the 5 mg dose have not been prospectively studied.
¶ Administer with a daily maintenance dose of aspirin of 75 to 100 mg.
# Take with antiplatelet doses of aspirin

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Anagrelide	No overall differences in response in the elderly; however, greater sensitivity cannot be ruled out.	Based on an OL, PK/PD study in 18 patients aged 7 to 16 years, no apparent differences in adverse events vs adults. Initiate at lower dose of 0.5 mg/day.	No dosage adjustments	For moderate hepatic impairment initiate dose at 0.5 mg/day and maintain for a minimum of 1 week with careful monitoring of CV effects. Avoid in severe impairment.	Pregnancy Category: C Unknown whether excreted in breast milk; discontinue nursing or discontinue drug.
DURLAZA (aspirin ER)	No overall differences in safety and efficacy have been observed between elderly and younger subjects.	Safety and efficacy have not been established. Due to aspirin, use is not recommended.	Avoid with severe renal failure	Avoid with severe hepatic dysfunction	Should be avoided during the third trimester of pregnancy, and 1 week prior to and during labor and delivery Due to potential for serious AEs in nursing infants, discontinue nursing or discontinue drug.
Cilostazol	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment. Dialysis patients have not been studied, but unlikely drug will be removed.	No dose adjustment required in mild hepatic impairment. Moderate or severe hepatic impairment have not been studied; dosing recommendations are not provided.	Pregnancy Category: C Reported in milk of animal models; discontinue nursing or discontinue drug
Clopidogrel	No dosage adjustment necessary	Safety and efficacy have not been established.	No dosage adjustment	No dosage adjustment	Pregnancy Category: B Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
Dipyridamole	No dosage adjustment	Safety and effectiveness in patients <12 years have not been established.	No dosage adjustment	No dosage adjustment; Elevations of liver enzymes have been reported.	Pregnancy Category: B Drug is excreted in breast milk; exercise caution

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EFFIENT (prasugrel)	Risk of bleeding increases with advancing age. Not recommended in patients 75 years and older except in high-risk situations[†]	Safety and efficacy have not been established. In a PC, RCT, the primary objective, reducing the rate of vaso-occlusive crisis, was not met in sickle-cell anemia patients aged 2 to 17 years.	No dosage adjustment	No dosage adjustment with mild to moderate hepatic impairment; Not studied in severe impairment, generally at higher risk of bleeding.	Pregnancy Category: B Unknown whether excreted in breast milk; use only if benefits outweigh risks
BRILINTA (ticagrelor)	No overall differences in safety and efficacy in patients 65 years and older. However, greater sensitivity of some older patients cannot be ruled out.	Safety and efficacy have not been established.	No dosage adjustment	Contraindicated with severe hepatic impairment; Consider carefully with moderate impairment; No dosage adjustment with mild impairment	Pregnancy Category: C Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
Ticlopidine	Clearance decreases with age. No overall differences in efficacy or safety were observed in elderly patients (mean age 70 years). However, greater sensitivity cannot be ruled out.	Safety and efficacy have not been established.	Dose reduction or discontinuation if hemorrhagic or hematopoietic issues occur with renal impairment	Dose adjustment may be needed; Not recommended with severe liver impairment.	Pregnancy Category: B Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
ZONTIVITY (vorapaxar)	In the TRA 2ºP – TIMI 50 study, 33% of patients were ≥65 years of age. The relative risk of bleeding was similar across groups. ZONTIVITY increases the risk of bleeding in proportion to the underlying risk. Older patients are generally at a higher risk of bleeding; consider patient age before initiating ZONTIVITY.	Safety and efficacy have not been established.	No dosage adjustments are required in patients with renal impairment.	No dosage adjustments are required in patients with mild to moderate hepatic impairment. ZONTIVITY is not recommended in patients with severe impairment due to increased risk of bleeding.	Pregnancy Category B Unknown whether excreted in breast milk. Discontinue nursing or drug because of the potential for serious effects

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Aspirin/ ER dipyridamole	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established. Due to aspirin, use is not recommended	Avoid aspirin with severe renal failure	Avoid with severe hepatic dysfunction	Pregnancy Category: D Drug is excreted in breast milk; exercise caution
YOSPRALA (aspirin DR/ omeprazole)	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established. Due to aspirin, use is not recommended	Avoid with severe renal failure	Avoid with any degree of hepatic impairment	Should be avoided during the third trimester of pregnancy, and 1 week prior to and during labor and delivery Due to potential for serious AEs in nursing infants, discontinue nursing or discontinue drug.

Abbreviations: CV=cardiovascular; OL=open label; PC=place-controlled; PD=pharmacodynamic; PK=pharmacokinetic; RCT=randomized-controlled trial
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.
† American College of Chest Physicians (ACCP) 2012 guidelines state that evidence suggests that neither prasugrel results in neither benefit nor harm in patients with age greater than 75 years.

CONCLUSION

- The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and CV diseases. Those agents which are available generically include anagrelide, cilostazol, clopidogrel, dipyridamole, ticlopidine, and aspirin/ER dipyridamole. Antiplatelet agents available only by brand name are BRILINTA (ticagrelor), DURLAZA (aspirin ER), EFFIENT (prasugrel), YOSPRALA (aspirin DR/omeprazole), and ZONTIVITY (vorapaxar).
- Antiplatelet agents have different sites of action. Aspirin is a COX-1 inhibitor. Ticlopidine, clopidogrel, and prasugrel irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Ticagrelor is a reversible inhibitor of $P2Y_{12}$. Vorapaxar is a first-in-class selective antagonist of the PAR-1, which is a receptor on thrombin. The mechanism of action of dipyridamole, anagrelide, and cilostazol are not completely understood, but each is believed to inhibit platelet aggregation. Clopidogrel has incomplete platelet inhibition, a slower onset of action, and poor response in some patients. Ticlopidine is generally not prescribed due to cases of rare but serious neutropenia (Micromedex, 2017).
- Clopidogrel has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. Study data has demonstrated that clopidogrel significantly reduced the risk of stroke, MI, and vascular death compared to aspirin in patients with a recent ischemic stroke, MI or established peripheral vascular disease. On the basis of the CURE, COMMIT, and CLARITY studies, clopidogrel received a FDA-approved indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions (Amsterdam et al, 2014; COMMIT, 2005; Culebras et al, 2014; CURE, 2001; Gerhard-Herman et al, 2016; January et al, 2014; O'Gara et al, 2013; Roffi et al, 2016; Sabatine et al, 2005a; Sabatine et al, 2005b).

- Clopidogrel's effectiveness is dependent on its conversion to its active metabolite mostly by CYP2C19. Patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, diminished antiplatelet responses, and generally exhibit higher CV event rates following MI than patients with normal CYP2C19 function. In addition, concomitant use of proton pump inhibitors, particularly those extensively inhibited by CYP2C19, with clopidogrel may also increase CV events.
- Prasugrel may be the most potent of these agents, with more desirable characteristics compared to clopidogrel with regard to drug-drug interactions and interpatient enzyme variability (Serebruany et al, 2009; Spinler, Rees, 2009; Wiviott et al, 2007). FDA-approval of prasugrel was based on the results from the TRITON-TIMI 38 study, which compared clopidogrel to prasugrel. Prasugrel has demonstrated efficacy in reducing ischemic events in patients with ACS who underwent PCI. Although compared to clopidogrel, there were no differences in the important outcomes of all-cause and CV mortality; and prasugrel demonstrated more major bleeding. The overall recommendation is for a thienopyridine to be used in ACS patients who are managed with PCI, with clopidogrel, prasugrel and ticagrelor listed as potential options. Of note, the use of prasugrel in STEMI patients with a prior history of stroke or TIA for which primary PCI is planned is not recommended (Levine et al, 2011; Levine et al, 2016b).
- Ticagrelor is FDA-approved to reduce the rate of thrombotic CV events in patients with ACS, including UA, NSTEMI, and STEMI. Ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel and ticlopidine). Ticagrelor is not a prodrug; therefore not subject to potential drug interactions associated with the other agents (Micromedex, 2017). PLATO was a pivotal clinical study establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic CV events in patients with ACS, which compared ticagrelor and clopidogrel in hospitalized patients with documented ACS, with or without ST-segment elevation. After 12 months of treatment, there was no difference in major bleeding; however, ticagrelor significantly reduced all-cause and CV mortality. This efficacy benefit was not observed in North American patients (Mahaffey et al, 2011; Wallentin et al, 2009). The PEGASUS TIMI-54 trial reinforced benefit in patients with a history of MI in which a reduction in the rate of CV death, MI and stroke was observed in patients treated with ticagrelor 60 mg twice daily plus aspirin over aspirin monotherapy. The rates of CV mortality or all-cause mortality alone were not significantly different between groups, and increased risk of major bleeding was observed with ticagrelor treatment (Bonaca et al, 2015).
- Clinical studies have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized studies comparing ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin (Gent et al, 1989; Gorelick et al, 2003; Hass et al, 1989). When compared to aspirin alone and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis following coronary stenting (Leon et al, 1998). Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.
- Vorapaxar is FDA-approved for use in patients with a history of MI or PAD. Vorapaxar should be prescribed with aspirin and/or clopidogrel according to their indications or standard of care, and not be used as monotherapy or concomitantly with warfarin or other anticoagulants. There is limited clinical experience with other antiplatelet drugs or with vorapaxar as a monotherapy agent. Increased hemorrhagic stroke and bleeding rates in patients with a history of stroke or TIA caused the vorapaxar phase 3 studies to be terminated early. In the TRA2°P-TIMI 50 trial, vorapaxar demonstrated lower rates of the composite of CV mortality, MI, or stroke vs placebo when added to standard antiplatelet therapy for secondary prevention of CV events in PAD or MI who have not undergone PCI. Significance was driven by MI reductions (Morrow et al, 2012; Tricoci et al, 2012; FDA Summary Review [ZONTIVITY], 2014; FDA Advisory Committee Transcript [ZONTIVITY], 2014).
    - When managing acute bleeding events, withholding vorapaxar may not be helpful because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of vorapaxar therapy also remain poorly defined (FDA Summary Review [ZONTIVITY], 2014; Morrow et al, 2012; Tricoci et al, 2012).
    - The 2016 ESC guidelines for CV disease prevention stipulate that vorapaxar cannot be recommended systematically in patients with stable atherosclerotic disease; however, the 2015 ESC guidelines state vorapaxar may be added to aspirin and clopidogrel for patients with a history of MI. The ESC acknowledges that efficacy is modest and must be weighed against the risk for bleeds (Piepoli et al, 2016; Roffi et al, 2016).
- Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo, but has not been shown to be more effective than aspirin (Diener et al, 1996; Leonardi-Bee et al, 2005). Aspirin plus ER dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with ER dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups (Diener et al, 1996). Aspirin plus ER dipyridamole significantly reduced the composite of death, nonfatal stroke

or MI and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache (ESPRIT, 2006).

- Cilostazol is used for the symptomatic treatment of intermittent claudication, and is recommended as an effective therapy to improve symptoms and increase walking distance in patients with claudication due to lower extremity PAD (Gerhard-Herman et al, 2016). Long-term effects of the drug on limb preservation and hospitalization have not been fully elucidated. Recent studies and systematic reviews have failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes when added to clopidogrel and aspirin therapy. Currently, experts generally do not recommend the use of cilostazol for the prevention of postprocedural complications in patients undergoing coronary artery stent placement, with the possible exception of those with an allergy or intolerance to aspirin or clopidogrel; in such cases, ACCP states that cilostazol may be used as a substitute for either aspirin or clopidogrel as part of the DAPT regimen (Alonso-Coello et al, 2012; Guyatt et al, 2012; Levine et al, 2011; Levine et al, 2016b).
- Anagrelide is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (Anagrelide study group, 1992; Birgegard et al, 2004; Dombi et al, 2017; Harrison et al, 2005; Penninga et al, 2004; Silver, 2005; Steurer et al, 2004; Wiviott et al, 2007).
- Aspirin is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared. Aspirin is the platelet inhibitor recommended as first-line in most treatment guidelines for general use, including initial management of noncardioembolic stroke or TIA, ACS, and MI, and for primary and secondary prevention in patients with cerebrovascular, CV, and peripheral vascular diseases (Amsterdam et al, 2014; Culebras et al, 2014; Gagne et al, 2013; Gerhard-Herman et al, 2016; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Kohli et al, 2014; O'Gara et al, 2013; Roffi et al, 2016; Smith et al, 2011; Smith et al, 2017). Evidence supporting the efficacy of aspirin has demonstrated a reduction in vascular death of ~15% and in nonfatal vascular events of ~30% (Eikelboom et al, 2012). In the US, nearly 40% of adults > 50 years of age use aspirin for the primary or secondary prevention of CV disease (Bibbins-Domingo et al, 2016).

- Antiplatelet therapy is recommended for a variety of indications:
    - Selection of $P2Y_{12}$ inhibitor therapy for patients with CAD varies greatly by individual patient characteristics and bleeding risks:
        - All guidelines agree and recommend long-term treatment with aspirin, or clopidogrel for those who cannot tolerate aspirin in patients with ACS (Amsterdam et al, 2014; Guyatt et al, 2012; January et al, 2014; Levine et al, 2011; Levine et al, 2016a; Levine et al, 2016b; O'Gara et al, 2013; Piepoli et al, 2016; Roffi et al, 2016).
        - The 2016 American College of Cardiology (ACC)/AHA guidelines for DAPT in patients with CAD have updated duration recommendations for 6 previously published guidelines based on data around newer generation stents. Recommendations range based on the benefit/risk profiles of CAD patients but overall, minimum courses of DAPT therapy are now recommended in certain patients. New key recommendations include: (1) clopidogrel therapy for a minimum of 6 months for patients treated with DES; (2) any $P2Y_{12}$ inhibitor treatment for 12 months in those with ACS; (3) extended DAPT continuation in patients who have low bleeding risk; and (4) shorter duration of DAPT for patients at lower ischemic risk with high bleeding risk and longer DAPT periods for patients at elevated ischemic risk with lower bleeding risk (Levine et al, 2016a).
        - The 2016 ESC guidelines updated recommendations on CV disease prevention. Key recommendations include: (1) in patients with ACS, DAPT with a $P2Y_{12}$ inhibitor (no agent recommended over another) and aspirin for 12 months is recommended, unless there are contraindications (e.g., excessive risk of bleeding); (2) a shorter duration of $P2Y_{12}$ inhibitor administration (ranging from 3 to 6 months) should be considered for patients with higher bleed risks after DES implantation; (3) in non-cardioembolic ischemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended; and (4) in patients with stable CAD, prasugrel is not recommended and ticagrelor is not recommended in stable CAD without a prior ACS (Piepoli et al, 2016).
        - Other guidelines include the ACCP which recommends general guidance of clopidogrel plus aspirin for 6 to 12 months in patients undergoing PCI and stent placement. Prasugrel should not be used in patients <60 kg, >75 years of age or with a prior history of stroke. In patients who are stopping anticoagulant therapy and do not have a contraindication to aspirin, it is recommended to administer aspirin over no aspirin to prevent recurrent venous thromboembolism (Guyatt et al, 2012; Kearon et al, 2016).

- The AHA/ACC and 2015 ESC guidelines for the management of patients with NSTEMI ACS provide more specific $P2Y_{12}$ inhibitor recommendations compared to other reputable society groups. For those patients with moderate to severe risk of ischemic events, DAPT with aspirin is recommended; however, ticagrelor is specifically recommended over clopidogrel for up to 12 months of treatment. Prasugrel is preferred over clopidogrel in post-PCI patients, except in those at high risk for bleeding. According to the 2015 ESC guidelines, vorapaxar may be added to aspirin and clopidogrel for patients with a history of MI, but efficacy is modest and must be weighed against the risk for bleeds (Amsterdam et al, 2014; January et al, 2014; O'Gara et al, 2013; Roffi et al, 2016).
- The 2011 AHA/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommends aspirin, or clopidogrel if aspirin is not tolerated, in all patients with CAD. A $P2Y_{12}$ inhibitor in combination with aspirin is recommended in patients after ACS or PCI with stent placement, while patients receiving a bare-metal stent or DES during PCI for ACS should be given clopidogrel, prasugrel, or ticagrelor for at least 12 months. Patients undergoing coronary artery bypass grafting, should be given aspirin for 1 year after surgery (Smith et al, 2011).

o The 2012 ACCP guidelines have included recommendations for aspirin monotherapy or aspirin/ER dipyridamole twice daily for initial therapy for TIA or ischemic stroke in order to prevent stroke (Guyatt et al, 2012). The AHA/ASA reinforce that the combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (Kernan et al, 2014). For minor ischemic stroke or TIA the combination of aspirin and clopidogrel might be reasonable, but adding antiplatelet therapy to vitamin K antagonist therapy is uncertain (January et al, 2014). Other guidelines state clopidogrel plus aspirin probably more effective at reducing stroke compared with aspirin monotherapy, but is less effective than warfarin (Culebras et al, 2014; Kernan et al, 2014). The 2014 AHA/ASA guidelines for the primary prevention of stroke state that current clinical data reflect risk but no benefit of aspirin for the prevention of a first stroke in the general population, and that there is no evidence that antiplatelet medications reduce the risk of stroke in the general population at low risk (Meschia et al, 2014). A 2017 AHA/ASA statement on the prevention of stroke in patients with silent cerebrovascular disease recommends that it is reasonable to avoid antiplatelet agents when there is no specific CV or cerebrovascular indication, but to otherwise to use them according to currently recommended indications (Smith et al, 2017). The 2011 AHA/ ACCF guidelines recommend that patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA should be given aspirin alone, clopidogrel alone, or a combination of aspirin plus ER dipyridamole (Smith et al, 2011).
o For the treatment of PAD, treatment with aspirin is recommended for asymptomatic disease, and aspirin or clopidogrel is recommended for secondary prevention of CV events in symptomatic PAD but not as dual therapy (Alonso-Coello et al, 2012; Smith et al, 2011). However, the 2011 ACC/AHA guidelines do state the combination of aspirin and clopidogrel may be considered to reduce the risk of CV events in patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity (Anderson et al, 2013). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend antiplatelet therapy with aspirin alone (75 to 325 mg per day) or clopidogrel alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD (Gerhard-Herman et al, 2016).
o The 2012 ACCP guidelines recommend the addition of cilostazol to aspirin or clopidogrel therapy in patients with refractory intermittent claudication who do not respond to conservative measures (Guyatt et al, 2012; Alonso-Coello et al, 2012). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend cilostazol as an effective therapy to improve symptoms and increase walking distance in patients with claudication (Gerhard-Herman et al, 2016).
o The 2017 AHA/ACC guidelines for the management of patients with valvular heart disease recommend antithrombotic therapy with aspirin in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis, and daily aspirin in all patients with a bioprosthetic aortic or mitral valve. Compared with oral anticoagulation alone, the addition of DAPT increases bleeding complications by at least 2- to 3-fold. Clopidogrel 75 mg daily may be a reasonable antithrombotic therapy option for the first 6 months after transcatheter aortic valve replacement (TAVR), in addition to life-long aspirin 75 mg to 100 mg daily (Nishimura, 2017).

- Due to the risk of GI complications, ACCF/ACG/AHA recommends that gastroprotective therapy be prescribed for the treatment and prevention of aspirin-associated GI injury in patients at sufficient risk. Proton pump inhibitors are considered the preferred gastroprotective agents over histamine-2 (H_2) receptor antagonists and misoprostol (Bhatt et al, 2008).
- The updated 2015 Beers Criteria published by the American Geriatric Society (AGS) recommends avoiding short-acting dipyridamole, ticlopidine, and cilostazol in certain elderly patients (AGS, 2015). The criteria also recommends against scheduled use of proton-pump inhibitors, such as omeprazole, for more than 8 weeks unless they are used for high-risk patients.

REFERENCES

- AGGRENOX prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. November 2015.
- AGRYLIN prescribing information. Shire US Inc. Wayne, PA. July 2015.
- Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e669S-90S.
- American Geriatrics Society (AGS). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015 Nov;63(11):2227-46.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23; 130(25):e344-426.
- Anagrelide Study Group. Anagrelide, a therapy for thrombocythemic states: experience in 577 patients. Am J Med. 1992;92:69-72.
- Anderson JL, Halperin JL, Albert N, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 March epub doi:10.1016/j.jacc2013.01.004.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71-86.
- Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 analysis. J Am Coll Cardiol. 2008;51(21):2028-33.
- Aradi D, Komocsi A, Vorobcsuk A, et al. Impact of clopidogrel and potent P2Y12-inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention. Systematic review and meta-analysis. Thromb Haemost 2013; 109(1):93-101.
- Banerjee S, Varghese C, Samuel J, et al. Comparison of the impact of short (<1 year) and long-term (≥1 year) clopidogrel use following percutaneous coronary intervention on mortality. Am J Cardiol. 2008;102:1159-62.
- Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011 Dec;32(23):2933-44.
- Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med. 1999; 159:2041-50.
- Bedenis R, Steward M, Cleanthis M, et al. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014; Issue 10. Art No. CD003748. Doi: 10.1002/14651858.CD003748.pub4.
- Bedenis R, Lethaby A, Maxwell H, et al. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. Cochrane Database Syst Rev. 2015; Issue 10. Art No. CD003748. Doi: 10.1002/14651858.CD003748.pub4.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017 Mar 7;135(10):e146-e603.
- Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS-TIMI 54. J Am Coll Cardiol. 2016 Jun 14;67(23):2732-40
- Bhatt DL, Fox KAA, Hacke W, et al; for the CHARISMA Investigators. Clopidogrel and aspirin vs aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354(16):1706-17.
- Bibbins-Domingo K, on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164(12):836-45.
- Birgegard G, Bjorkholm M, Kutti J, et al. Adverse effects and benefits of two years of anagrelide treatment for thrombocythemia in chronic myeloproliferative disorders. Haematologica. 2004;89:520-7.
- Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016 Sep 6;134(10):e156-78. doi: 10.1161/CIR.0000000000000405.
- Bohula EA, Aylward PE, Bonaca MP, et al. Efficacy and safety of vorapaxar with and without a theienopyridine for secondary prevention in patients with previous myocardial infarction and no history of stroke or transient ischemic attack: Results from TRA 2ºP-TIMI 50. Circulation. 2015;132:1871-79.
- Bohula EA, Bonaca MP, Braunwald E et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. Circulation. 2016 Jul 26;134(4):304-13. doi: 0.1161/CIRCULATIONAHA.115.019861.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction (PEGASUS-TIMI 54). N Engl J Med. 2015; 372(19):1791.
- Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA 2˚P-TIMI 50. Circulation. Apr 9, 2013;127(14):1522-9.
- BRILINTA prescribing information. AstraZeneca. Wilmington, DE. July 2016.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Jul;45(7):2160-236.

- Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study. Lancet. 2010 Jan 23;375(9711):283-93.
- CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel vs aspirin in patients at risk of ischemic events (CAPRIE). Lancet. 1996;348(9038):1329-39.
- COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. Lancet. 2005;366:1607-21.
- Culebras A, Messe SR, Chaturvedi S, et al. Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. Feb 25, 2014;82(8):716-24.
- The CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.
- Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000; 109:523-30.
- De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular diseases. Cochrane Database Syst Rev. 2007;(3):CD001820. DOI: 10.1002/14651858.CD001820.pub3.
- Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared to clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. Lancet. 2004;364:331-7.
- Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci. 1996;143(1-2):1-13.
- Dombi P, Illés Á, Demeter J, et al. Anagrelide reduces thrombotic risk in essential thrombocythaemia vs. hydroxyurea plus aspirin. Eur J Haematol. 2017 Feb;98(2):106-111. doi: 10.1111/ejh.12806.
- Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, et al. Coronary stent restenosis in patients treated with cilostazol. Circulation. 2005; 112:2826-32.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 9, 2017.
- DURLAZA prescribing information. New Haven Pharmaceuticals, Inc. North Haven, CT. September 2015.
- EFFIENT prescribing information. Eli Lilly and Company. Indianapolis, IN. July 2016.
- Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(suppl 2):e89S-e119S.
- Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet. 2015 Feb 28;385(9970):792-8.
- ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole vs aspirin alone after cerebral ischemia of arterial origin (ESPRIT): a randomized controlled trial. Lancet. 2006;367(9523):1665-73.
- Fanari Z, Malodiya A, Weiss SA, et al. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: Meta-analysis of randomized controlled trials. Cardiovasc Revasc Med. 2017 Jan - Feb;18(1):10-15. doi: 10.1016/j.carrev.2016.07.006
- FDA Advisory Committee Transcript (ZONTIVITY). Transcript for the January 15, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee. January 15, 2014. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM396033.pdf. Accessed March 15, 2017.
- FDA Summary Review for Regulatory Action. ZONTIVITY. April 18, 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204886Orig1s000SumR.pdf. Accessed March 15, 2017.
- Fihn SD, Gardin JM, Abrams J, et al. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: Executive Summary. Circulation. 2012;126:3097-3137.
- Gagne JJ, Bykov K, Choudhry NK, et al. Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison. BMJ. Sept 17, 2013;347:f5307.
- Gent M, Blakely JA, Easton JD, et al. The Canadian American ticlopidine study (CATS) in thromboembolic stroke. Lancet. 1989;1(8649):1215-20.
- Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016 Nov 8. pii: S0735-1097(16)36902-9. doi:10.1016/j.jacc.2016.11.007.
- Goldstein JL, Whellan DJ, Scheiman JM, et al. Long-term safety of a coordinated delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg for secondary cardiovascular disease prevention in patients at GI risk. Cardiovasc Ther. 2016;34(2):59-66.
- Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. JAMA. 2003;289(22):2947-57.
- Gouya G, Arrich J, Wolzt M, et al. Antiplatelet treatment for prevention of cerebrovascular events in patients with vascular diseases: a systematic review and meta-analysis. Stroke. 2014 Feb;45(2):492-503.
- Guyatt GH, Akl EA, Crowther M, et al; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):7S-47S.
- Harrington RA, Becker RC, Cannon CP, et al. Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th edition). Chest. 2008;133(6 Suppl):776S-814S.
- Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared to anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005;353:33-45.
- Hass W, Easton J, Adams H, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study (TASS) Group. N Engl J Med. 1989;8(321):501-7.
- Held C, Asenblad N, Bassand JP, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011 Feb 8;57(6):672-84.
- Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001; 344:1608-21.
- Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med. 2017 Jan 5;376(1):32-40. doi: 10.1056/NEJMoa1611688.

- Husted S, James SK, Bach RC, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, platelet inhibition and patient outcomes (PLATO) trial. Eur Heart J. 2014;35(23):1541-50.
- James S, Angiolillo DJ, Corenal JH, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndrome and diabetes: a substudy from the platelet inhibition and patient outcomes (PLATO) trial. Eur Heart J. 2010a;31:3006-16.
- James S, Budaj A, Aylward P, et al. Ticagrelor vs clopidogrel in acute coronary syndromes in relation to renal function: results from the platelet inhibition and patient outcomes (PLATO) trial. Circulation. 2010b;122:1056-67.
- James SK, Roe MT, Cannon CP, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ. 2011 Jun 17;342:d3527.
- January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary. Circulation. 2014 Dec 2;130(23):2071-104. .
- Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jan;44:870-947.
- Johnston SC, Amarenco P, Albers GW, et al for the SOCRATES Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016 Jul 7;375(1):35-43.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):293-294.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Jul;45(7):2160-236.
- Kohli P, Wallentin L, Reyes E, et al. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO study. Circulation. Feb 12, 2013;127(6):673-80.
- Kohli P, Udell JA, Murphy SA, et al. Discharge aspirin dose and clinical outcomes in patients with acute coronary syndromes treated with prasugrel vs clopidogrel: an analysis from the TRITON-TIMI 38 study (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38). J Am Coll Cardiol. Jan 28, 2014;63(3):225-32.
- Kunishima T, Musha H, Eto F, et al. A randomized trial of aspirin vs cilostazol therapy after successful coronary stent implantation. Clin Ther. 1997; 19:1058-66.
- Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e601S-36S.
- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339(23):1665-71.
- Leonardi-Bee J, Bath PMW, Bousser MG, et al. Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. Stroke. 2005;36(1):162-8.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. J Am Coll Cardiol. 2011 Dec 6;58(24):e44-122.
- Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the society for cardiovascular angiography and interventions. Circulation. 2016b Mar 15;133(11):1135-47.
- Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation. 2016a Sep 6;134(10):e123-55.
- Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared to clopidogrel by geographic region in the platelet inhibition and patient outcomes (PLATO) trial. Circulation. 2011;124:544-54.
- Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. Nov 2014;371: 2155-66.
- Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Dec;45(12):3754-832. doi: 10.1161/STR.0000000000000046.
- Melloni C, Jones WS, Washam JB, et al. Antiplatelet and anticoagulant treatments for unstable angina/non-ST elevation myocardial infarction. Rockville MD: Agency for Healthcare Research and Quality; Nov 2013. Report No: 13(14)-EHC125-EF.
- Micromedex® Solutions [database on the Internet]. Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com/home/dispatch. Accessed March 14, 2017.
- Money SR, Herd A, Isaacsohn JL et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Surg. 1998; 27:267-75.
- Montalescot G, Wiviott SD, Murphy SA, et al. Prasugrel compared to clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double blind, randomized controlled trial. Lancet. 2009;373:723-31.
- Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events (TRA 2°P-TIMI 50). N Engl J Med. April 12, 2012;366(15):1404.
- Mulukutla SR, Marroquin OC, Vlachos HA, et al. Benefit of long-term dual anti-platelet therapy in patients treated with drug-eluting stents: from the NHLBI dynamic registry. Am J Cardiol. 2013 Feb 15;111(4):486-92. doi: 10.1016/j.amjcard.2012.10.030.
- Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared to clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J. 2008;29:2473-9.
- Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomized controlled trials. BMJ. 2015 Apr 16;350:h1618.

- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2017 Mar 15. doi: 10.1161/CIR.0000000000000503. [Epub ahead of print]
- O'Donnell ME, Badger SA, Sharif MA, et al. The vascular and biochemical effects of cilostazol in patients with peripheral arterial disease. J Vasc Surg. 2009a May;49(5):1226-34.
- O'Donnell ME, Badger SA, Sharif MA, et al. The effects of cilostazol on exercise-induced ischaemia-reperfusion injury in patients with peripheral arterial disease. Eur J Vasc Endovasc Surg. 2009b Mar;37(3):326-35.
- O'Donoghue M, Antman EM, Braunwald E, et al. The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention. J Am Coll Cardiol. 2009;54:678-85.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary. Circulation. 2013:127:529-555.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 9, 2017.
- Park SW, Lee CW, Kim HS, et al. Comparison of cilostazol vs ticlopidine therapy after stent implantation. Am J Cardiol. 1999; 84:511-4.
- Park SW, Lee CW, Kim HS, et al. Effects of cilostazol on angiographic restenosis after coronary stent placement. Am J Cardiol. 2000; 86:499- 503.
- Penninga E, Jensen BA, Hansen PB, et al. Anagrelide treatment in 52 patients with chronic myeloproliferative diseases. Clin Lab Haem. 2004;26:335-40.
- PERSANTINE prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2011.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;37(29):2315-81.
- PLAVIX prescribing information. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Bridgewater, NJ. September 2016.
- PLETAL prescribing information. Otsuka Pharmaceutical Co., LTD. Rockville, MD. January 2016.
- Powers WJ, Derdeyn CP, Biller J, et al. 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. Stroke.2015 Oct;46(10):3020-35.
- Pride YB, Wiviott SD, Buros JL, et al. Effect of prasugrel vs clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a trial to assess improvement in therapeutic outcomes by optimizing platelet inhibitor with prasugrel (TRITON)-thrombolysis in myocardial infarction (TIMI) 38 substudy. Am Heart J. 2009;158:e21-6.
- Rafique AM, Nayyar P, Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. JACC Cardiovasc Interv. 2016 May 23;9(10):1036-46. doi: 10.1016/j.jcin.2016.02.013.
- Reilly MP, Mohler ER. Cilostazol: treatment of intermittent claudication. Ann Pharmacother. 2001; 35:48-56.
- Roe MT, Armstrong PW, Fox KAA, et al. Prasugrel vs clopidogrel for acute coronary syndromes without revascularization. NEJM. 2012;367:1297-1309.
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management for acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315. doi: 10.1093/eurheartj/ehv320
- Sabatine MS, Cannon CP, Gibson CM, et al; the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY Study. N Engl J Med. 2005a;294(10):1224-32.
- Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005b;352(12):1179-89.
- Schömig A, Kastrati A, Wessely R. Prevention of restenosis by systemic drug therapy: back to the future? Circulation. 2005;112; 2759-2761.
- Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. Lancet. Oct 13, 2012;380(9850):1317-24.
- Serebruany V, Shalito I, Kopyleva O. Prasugrel development-Claims and achievements. Thromb Haemost. 2009;101:14-22.
- Sharma A, Helft G, Garg A et al. Safety and efficacy of vorapaxar in secondary prevention of atherosclerotic disease: A meta-analysis of randomized control trials. Int J Cardiol. 2017 Jan 15;227:617-624. doi: 10.1016/j.ijcard.2016.10.088.
- Silver RT. Anagrelide is effective in treating patients with hydroxyurea-resistant thrombocytosis in patients with chronic myeloid leukemia. Leukemia. 2005;19:39-43.
- Smith SC, Benjamin EJ Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.
- Smith EE, Saposnik G, Biessels GJ, et al. Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2017 Feb;48(2):e44-e71. doi: 10.1161/STR.0000000000000116.
- Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. J Manage Care Pharm. 2009;15(5):383-95.
- Steg PG, James S, Harrington RA, et al. Ticagrelor vs clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010 Nov 23;122(21):2131-41.
- Steurer M, Gastl G, Jedrzejczak WW, et al. Anagrelide for thrombocytosis in myeloproliferative disorders. Cancer. 2004;101(10):2239-46.
- Storey RF, Becker RC, Harrington RA, et al. Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the Platelet Inhibition and Patients Outcomes [PLATO] Pulmonary Function Substudy). Am J Cardiol. 2011;108:1542-6.
- Take S, Matsutani M, Ueda H, et al. Effect of cilostazol in preventing restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol. 1997; 79:1097-9.

- Ticlopidine prescribing information. Carilion Materials Management for Teva Pharmaceuticals. Sellersville, PA. August 2016.
- Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes (TRACER trial). N Engl J Med. Jan 5, 2012;366(1):20-33.
- Tsuchikane E, Fukihara A, Kobayashi T, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. Circulation. 1999; 100:21-6.
- Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016 Jan 21;37(4):390.
- Vandvik PO, Lincoff M, Gore JM, et al. Primary and secondary prevention of cardiovascular disease. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(suppl 2):e637S-e668S.
- Varenhorst C, Alstrom U, Braun O, et al. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. Heart. 2014; 100(22):1762-9.
- Valgimigli M, Campo G, Monti M, et al. Short versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial (PRODIGY). Circulation. 2012;125:2015–2026.
- Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. Heart. 2016 Apr;102(8):617-25. doi: 10.1136/heartjnl-2015-308963.
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045-57.
- Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor vs clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010 Oct 16;376(9749):1320-8.
- Wang Y, Minematsu K, Wong KS, et al. Ticagrelor in acute stroke or transient ischemic attack in Asian patients: from the SOCRATES trial (acute stroke or transient ischemic attack treated with aspirin or ticagrelor and patient outcomes). Stroke. 2017 Jan;48(1):167-173. doi: 10.1161/STROKEAHA.116.014891.
- Whellan DJ, Goldstein JL, Cryer BL, et al. PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: results of two 6-month, phase 3 studies. Am Heart J. 2014;168(4):495-502.
- Wiviott SD, White HD, Ohman EM, et al. Prasugrel vs clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TILOGY ACS trial. Lancet. July 2013:382:605-13. Correction published 30 Aug, 2013.
- Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel thrombolysis in myocardial infarction 38. Circulation. 2008a;118:1626-36.
- Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomized trial. Lancet. 2008b;371:1353-63.
- Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel vs clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.
- Wiviott SD, Trenk D, Frelinger AL, et al; PRINCIPLE-TIMI 44 Investigators. Prasugrel compared to high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation Thrombolysis in Myocardial Infarction 44 trial. Circulation. 2007;116(25):2923-32.
- Xu LX, Chen KY, Liu T et al. Adjunctive loading dose of cilostazol in preventing periprocedural myocardial infarction. Cardiovasc Ther. 2016 Aug;34(4):225-33. doi: 10.1111/1755-5922.12192.
- Yoon YS, Shim WH, Lee DH, et al. Usefulness of cilostazol vs ticlopidine in coronary artery stenting. Am J Cardiol. 1999; 84:1375-80.
- YOSPRALA prescribing information. Aralez Pharmaceuticals US, Inc. Princeton, NJ. October 2016.
- Zhang Y, Zhao Y, Pang M, et al. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. Acta Cardiol. 2016 Jun;71(3):309-16. doi: 10.2143/AC.71.3.3152091.
- ZONTIVITY prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. April 2015.
- Zou Y, Hu C, Ye W, et al. Long-term clinical efficacy and safety of adding cilostazol to dual antiplatelet therapy after drug-eluting stent implantation in coronary arteries: A meta-analysis of randomized controlled trials. Thromb Res. 2015 Nov;136(5):870-7. doi: 10.1016/j.thromres.2015.08.018.

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Therapeutic Class Overview
Growth Hormone

INTRODUCTION

- Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Another physiological effect of GH is stimulation of cartilage growth (Molitch et al, 2011).
- Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A patient's growth patterns are compared to the established norms. The clinical manifestations of GHD will vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients will present with early severe growth failure, delayed bone age, central disposition of body fat and very low serum concentrations of GH, insulin-like growth factor 1 (IGF-1) and IGF binding protein-3. These patients are also more prone to hypoglycemia, prolonged jaundice, microphallus in males and giant cell hepatitis. GHD in pediatric patients with partial deficiency may be more difficult to diagnose, as these manifestations may not be as obvious (Molitch et al, 2011).
- Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated and continued until cessation of linear growth. Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age (Molitch et al, 2011).
- Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous (SC) injection, are currently the most widely utilized. Due to the variability in individual response to therapy, after initial dosing, the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. A patient's growth velocity, as compared to a similar population, should also be monitored to determine if the growth response is adequate (Molitch et al, 2011).
- Possible explanations for an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH, or concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 centimeters per year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood (Molitch et al, 2011).
- The majority of pediatric patients with idiopathic, isolated GHD in their childhood will have normal GH secretion during late adolescence and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies, and/or those with structural defects in the hypothalamic-pituitary region rarely recover the ability to secrete GH as an adult. Therefore, retesting may not be required (Molitch et al, 2011).
- GHD may also occur in adult patients. Fifteen to 20 percent of adult-onset GHD represents the continuation of childhood-onset GHD into maturity; the remainder is adult-onset acquired from damage to the pituitary gland or hypothalamus. GHD is associated with increased metabolic syndrome, increased cardiovascular morbidity and mortality rates, reduced lean body mass, increased abdominal adiposity, early atherosclerosis, dyslipidemia, coagulation abnormalities, insulin resistance, decreased bone mineral density, and a decreased quality of life (Mathioudakis and Salvatori, 2008). The role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults is not as well established and includes improvement in bone mineral density, sense of well-being, muscle strength and lipid profile. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood-onset or adult-onset (Molitch et al, 2011).
- All of the GH preparations contain somatropin, otherwise known as recombinant human GH. The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease (CKD), Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene, and Noonan syndrome, as well as for idiopathic short stature.

- The majority of preparations are also indicated for the treatment of GHD in adults. Of note, SEROSTIM® is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults. In addition, ZORBTIVE® is approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support. Specific FDA-approved indications for the various GH preparations are outlined in Table 2. All of the available GH preparations are available for SC injection and there are currently no generics available within the class.
- Growth hormone preparations are available in various formulations, and several delivery devices are available. The dosing device may be a factor in patient adherence with the prescribed regimen.
- Medispan Class: Growth Hormones

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
GENOTROPIN®	Pharmacia & Upjohn	08/24/1995	-
HUMATROPE®	Eli Lilly	03/08/1987	-
NORDITROPIN®	Novo Nordisk	06/20/2000	-
NUTROPIN AQ®	Genentech	12/29/1995	-
OMNITROPE®	Sandoz	05/30/2006	-
SAIZEN®	EMD Serono	10/08/1996	-
SEROSTIM	EMD Serono	08/23/1996	-
ZOMACTON™*	Ferring Pharmaceuticals	01/04/2002	-
ZORBTIVE	EMD Serono	12/01/2003	-

*In March 2015, Ferring Pharmaceuticals received approval for changing the name of their product TEV-TROPIN to ZOMACTON (PR Newswire, 2015).

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	GENOTROPIN	HUMATROPE	NORDITROPIN	NUTROPIN AQ	OMNITROPE	SAIZEN	SEROSTIM	ZOMACTON	ZORBTIVE
Growth failure associated with chronic renal insufficiency before renal transplant				✔					
Growth failure associated with Noonan syndrome			✔						
Growth failure associated with Prader-Willi syndrome	✔				✔				
Growth failure associated with short-stature homeobox-containing gene deficiency		✔							
Growth failure associated with Turner syndrome	✔	✔	✔	✔	✔				
Growth failure in children born small for gestational age	✔	✔	✔		✔				
Growth hormone deficiency	✔	✔	✔	✔	✔	✔		✔	
Idiopathic short stature	✔	✔		✔	✔				
Human immunodeficiency virus-associated wasting or cachexia							✔		
Treatment of short bowel syndrome in patients receiving nutritional support									✔

(Prescribing information: GENOTROPIN, 2016; HUMATROPE, 2016; NORDITROPIN, 2016; NUTROPIN AQ, 2016; OMNITROPE, 2016; SAIZEN, 2017; SEROSTIM, 2016; ZOMACTON, 2016; ZORBTIVE, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are limited head-to-head clinical trials comparing different GH preparations to one another.
- Clinical trials to support the use of GH for the treatment of growth failure associated with chronic renal insufficiency before renal transplant and Noonan syndrome in pediatric patients are limited (Fine et al, 1995; Noordam et al, 2001; Santos et al, 2010; Vimalachandra et al, 2006). For the treatment of growth failure associated with chronic renal insufficiency, a Cochrane Review of 15 randomized controlled trials demonstrated that after one year of treatment with GH (28 international units/m^2/week), height velocity increased 3.8 cm/year more than no treatment. The duration of the trials was not long enough to determine if continuing treatment with GH resulted in an increase in final adult height (Vimalachandra et al, 2006). In addition, a randomized controlled trial evaluating GH in patients with Noonan syndrome found a positive effect of GH on linear growth. Specifically, there was a significantly greater change in height standard deviation score and bone maturation was accelerated with GH compared to no treatment. In this trial, data also suggests that once treatment with GH is discontinued, "catch-down" (artificially stimulated growth declines once GH is discontinued) growth can occur (Noordam et al, 2001).
- Clinical trials consistently demonstrate the significant benefits of GH in pediatric patients with Prader-Willi syndrome in accelerating growth and in improving body composition. Benefits were also observed in improving bone mineral density, lipid profiles, energy expenditure, strength and agility, and pulmonary function (Carrel et al, 1999; Carrel et al, 2004; Festen et al, 2008; Lindgren et al, 1997; Lindgren et al, 1998; Lindgren et al, 1999; Myers et al, 1999; Myers et al, 2007). Data from one trial suggests that growth velocity declines dramatically once treatment is discontinued (Lindgren et al, 1997).
- HUMATROPE demonstrated efficacy in increasing first-year height velocity in patients with Short Stature Homeobox-containing gene deficiency when compared to no treatment (P<0.0001) (Blum et al, 2007).
- Several clinical trials consistently demonstrate that GH significantly increases the growth rate of pediatric patients with Turner syndrome. Overall, various dose ranging trials did not consistently demonstrate a superior weight-based GH dosing regimen over another; all doses of GH were beneficial. In addition, data suggest that increases in height are greatest during the first year of therapy (Baxter et al, 2007; Bertrand et al, 1996; Massa et al, 1995; Nienhuis et al, 1993; Sas et al, 1999a; Takano et al, 1989a; Takano et al, 1989b; Takano et al, 1989c; Takano et al, 1993; Takano, 1995; van Pareren et al, 2003; van Teunenbroek et al, 1996). A Cochrane Review of four randomized controlled trials demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short-term growth in patients with Turner syndrome by approximately three centimeters during the first year of treatment. Despite the increase, the final height achieved was still below the normal range (Baxter et al, 2007).
- For the treatment of growth failure in pediatric patients born small for gestational age, clinical trials again consistently demonstrate the significant benefits of GH on increasing growth rates (Arends et al, 2003; Bannink et al, 2010; Boguszewski et al, 1998; Bozzola et al, 2004; Chatelain et al, 1994; de Zegher et al, 1996; de Zegher et al, 2005; De Schepper et al, 2008; Jung et al, 2009; Maiorana et al, 2009; Sas et al, 1999b). Data from individual clinical trials and three meta-analyses demonstrate that response to GH therapy is dose-dependent, and higher doses of GH result in additional gain (de Zegher et al, 1996; de Zegher et al, 2005).
- Treatment with GH has been shown to increase height velocity in both prepubertal and pubertal pediatric patients with GHD (Coelho et al, 2008; Cohen et al, 2002; de Muinck Keizer-Schrama et al, 1992; Kristrom et al, 2009; MacGillivray et al, 1996; Mauras et al, 2000; Romer et al, 2009; Sas et al, 2010; Shih et al, 1994; Wilson et al, 1985). Two head-to-head trials have demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared three GH preparations (GENOTROPIN, HUMATROPE and SAIZEN), while the second evaluated two preparations (GENOTROPIN and OMNITROPE) (Romer et al, 2009; Shih et al, 1994).
- In pediatric patients with idiopathic short stature, somatropin has been shown to increase first-year growth velocity and final height (Albertsson-Wikland et al, 2008; Bryant et al, 2007; Finkelstein et al, 2002; Hopwood et al 1993; Kristrom et al, 2009; van Gool et al, 2010; Wit et al, 2005). Additionally, once daily compared to three times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity (Bryant et al, 2007; Finkelstein et al, 2002).
- Several placebo-controlled, randomized trials have demonstrated the efficacy of GH in improving body composition and lipid profiles in adult patients with GHD (Abrahamsen et al, 2002; Abrahamsen et al, 2004; Arwert et al, 2005; Arwert et al, 2006; Attanasio et al, 2004; Attanasio et al, 2005; Beauregard et al, 2008; Bell et al, 2004; Burman et al,

1997; Chihara et al, 2004; Chihara et al, 2005; Chihara et al, 2006; Chihara et al, 2008a; Chihara et al, 2008b; Chipman et al,1997; Colao et al, 2005; Conway et al, 2009; Cuneo et al, 1993; Davidson et al, 2004; Drake et al, 2003; Eden et al, 1993; Elgzyri et al, 2004; Falleti et al, 2006; Gilchrist et al, 2002; Gomez et al, 2000; Hoffman et al, 2004a; Hoffman et al, 2004b; Holmes et al, 1995; Hwu et al, 1997; Janssen et al, 1998; Kehely et al, 2002; Leese et al, 1998; Maison et al, 2003; Mauras et al, 2005; McGauley et al, 1990; Newman et al, 2011; Nolte et al, 1997; Rahim et al, 1998; Rosenfalck et al, 1999; Rubeck et al, 2009; Russell-Jones et al, 1994; Sesmilo et al, 2000; Shalet et al, 2003; Sneppen et al, 2002; Snyder et al, 2007; Underwood et al, 2003; Vahl et al, 2000; Verhelst et al, 1997; Weaver et al, 1995; Webster et al, 1997; Widdowson et al, 2010; Yuen et al, 2005). Furthermore, results from meta-analyses and randomized controlled trials have demonstrated that treatment with GH was associated with improved cardiac function and bone mineral density (Barake et al, 2014; Davidson et al, 2004; Maison et al, 2003). However, there are currently conflicting data with regard to the effect of GH on cognitive function, quality of life and exercise capacity (Arwert et al, 2005; Falleti et al, 2006; Rubeck et al, 2009; Widdowson, 2010).

- In patients with human immunodeficiency virus-associated wasting, SEROSTIM has been shown to increase body weight, lean body mass and work output. However, effects on quality of life were variable (Moyle et al, 2004; Schambelan et al, 1996).
- A meta-analysis assessing the safety and efficacy of GH with or without glutamine supplementation for adult patients with short bowel syndrome was conducted. Five studies were included in the review. Human GH with or without glutamine appears to provide benefit in terms of increased weight (median [MD] 1.66 kg; 95% confidence interval [CI], 0.69 to 2.63; P=0.0008), lean body mass (MD 1.93 kg; 95% CI, 0.97 to 2.9; P=0.0001), energy absorption (MD 4.42 Kcal; 95% CI, 0.26 to 8.58; P=0.04) and nitrogen absorption (MD 44.85 g; 95% CI, 0.2 to 9.49; P=0.04) for patients with short bowel syndrome. One randomized controlled trial focused on parenteral nutrition (PN) requirements and demonstrated decreased PN volume and calories and number of infusions in patients who received GH with or without glutamine supplementation. Only patients who received GH with glutamine maintained statistically significant PN reductions at three-month follow-up. The results suggest a positive effect of GH on weight gain and energy absorption. After cessation of therapy, however, the effects return to baseline in the majority of the trials (Wales et al, 2010).
- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Noonan syndrome, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency (Bondy et al, 2007; Cohen et al, 2008; Deal et al, 2013; Goldstone et al, 2008; Grimberg et al, 2016; National Kidney Foundation, 2009). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utilized.
- For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD (Cook et al, 2009). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (Cook et al, 2009; Molitch et al, 2011). The 2009 American Association of Clinical Endocrinologists Guidelines indicate that no evidence exists to support any specific growth hormone product over another (Cook et al, 2009).

SAFETY SUMMARY

- Contraindications: Active malignancy, diabetic retinopathy, hypersensitivity to the agent or any of its excipients, acute respiratory failure, treatment of patients with acute critical illness, and do not use for growth promotion in patients with closed epiphyses.
- Key Warnings/Precautions:
    - Somatropin may increase progression or recurrence of intracranial neoplasms particularly meningiomas in patients treated with radiation to the head for their first neoplasm.
    - Undiagnosed or untreated hypothyroidism may impair optimal response to somatropin.
    - Somatropin may decrease insulin sensitivity, and previously undiagnosed diabetes mellitus may be unmasked during treatment.
    - Slipped capital femoral epiphyses and scoliosis can occur in pediatric patients.
    - Fluid retention has been associated with somatropin in adult patients.
    - Increases in serum levels of inorganic phosphorous, alkaline phosphatase, parathyroid hormone and insulin-like growth factor-1 may occur.
    - Tissue atrophy may occur when somatropin is administered SC at the same site over a long period of time.
    - Somatropin may reduce serum cortisol levels or unmask central hypoadrenalism in patients at risk for pituitary hormone deficiency.
- Adverse Drug Events: Nerve, muscle, or joint pain, edema, carpal tunnel syndrome, numbness and tingling of the skin, high cholesterol levels, and injection site reactions.
- Drug Interactions: Estrogens, glucocorticoids, and insulin or other hypoglycemic agents.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
GENOTROPIN	Cartridge, powder for reconstitution: 5 mg, 12 mg; contains preservative MINIQUICK® syringe device: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, 2 mg; preservative-free	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then increase every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.04 mg/kg/week SC divided into six or seven doses, then increase every four to eight weeks to not more than 0.08 mg/kg/week based on the clinical response, adverse effects and serum IGF-I concentrations Pediatric Growth failure associated with Prader-Willi syndrome: 0.24 mg/kg/week SC divided into six or seven doses Growth failure associated with Turner syndrome: 0.33 mg/kg/week SC divided into six or seven doses Growth failure in children born small for gestational age: up to 0.48 mg/kg/week SC divided into six or seven doses Growth hormone deficiency: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses	Give in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Idiopathic short stature: up to 0.47 mg/kg/week SC divided into six or seven doses	
HUMATROPE	Cartridge, powder for reconstitution: 6 mg, 12 mg, 24 mg Vial, powder for reconstitution: 5 mg	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.0125 mg/kg/day Pediatric Growth failure associated with short-stature homeobox-containing gene deficiency: 0.05 mg/kg SC daily (0.35 mg/kg/week) Growth failure associated with Turner syndrome: up to 0.054 mg/kg SC daily (0.375 mg/kg/week) Growth failure in children born small for gestational age: up to 0.067 mg/kg SC daily (0.47 mg/kg/week) Growth hormone deficiency: 0.026 to 0.043 mg/kg SC daily (0.18 to 0.3 mg/kg/week) Idiopathic short stature: up to 0.053 mg/kg SC daily (0.37 mg/kg/week)	Administer only by SC injection with regular rotation of injection sites to avoid lipoatrophy.
NORDITROPIN	Prefilled pen (NORDITROPIN FLEXPRO®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL 30 mg/3 mL	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), not more than 0.004 mg/kg SC daily, then adjust after six weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.016 mg/kg/day Pediatric Growth failure associated with Noonan syndrome: up to 0.066 mg/kg SC daily Growth failure associated with Turner syndrome: up to 0.067 mg/kg SC daily Growth failure in children born small for gestational age: up to 0.067 mg/kg SC daily	Rotate injection site to avoid lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Growth hormone deficiency: 0.024 to 0.034 mg/kg SC daily, six to seven times a week	
NUTROPIN AQ	Prefilled cartridge (NUTROPIN AQ NUSPIN®): 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.025 mg/kg/day in patients ≤35 years old and 0.0125 mg/kg/day in patients >35 years old Pediatric Growth failure associated with chronic renal insufficiency before renal transplant: up to 0.35 mg/kg/week SC divided into daily doses, continue up to the time of renal transplantation Growth failure associated with Turner syndrome: up to 0.375 mg/kg/week SC divided into three to seven doses Growth hormone deficiency: up to 0.3 mg/kg/week SC divided into daily doses; up to 0.7 mg/kg/week divided daily may be used in pubertal patients Idiopathic short stature: up to 0.3 mg/kg/week SC divided into daily doses	Inject in the thigh, upper arm, abdomen, or buttock. Always rotate to avoid lipoatrophy.
OMNITROPE	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.04 mg/kg/week SC divided into daily doses, then adjust every four to eight weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.08 mg/kg/week Pediatric Growth failure associated with Prader-Willi syndrome: 0.24 mg/kg/week SC divided into six or seven doses Growth failure associated with Turner syndrome: 0.33 mg/kg/week SC divided into six to seven doses	Dose should be given daily by SC injection (administered preferably in the evening). Administer in the thigh, buttocks, or abdomen. Always rotate injection sites to prevent lipoatrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		Growth failure in children born small for gestational age: up to 0.48 mg/kg/week SC divided into six or seven doses Growth hormone deficiency: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Idiopathic short stature: 0.47 mg/kg/week SC divided into six or seven doses	
SAIZEN	Cartridge, powder for reconstitution: 8.8 mg (click.easy) Vial, powder for reconstitution: 5 mg (15 IU) 8.8 mg (26.4 IU)	Adult Growth hormone deficiency: Initial (non-weight based), 0.15 to 0.3 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.005 mg/kg SC daily, then adjust after four weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.01 mg/kg/day after four weeks depending on patient's tolerance Pediatric Growth hormone deficiency: 0.18 mg/kg/week SC or IM divided into three, six or seven doses	
SEROSTIM	Vial, powder for reconstitution: 4 mg (12 IU) Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) 6 mg (18 IU)	Adults Human immunodeficiency virus-associated wasting or cachexia: SC at bedtime with the following weight-based dosage: body weight <35 kg, 0.1 mg/kg/day; 35 to 45 kg, 4 mg/day; 45 to 55 kg, 5 mg/day; >55 kg, 6 mg/day; maximum, 6 mg/day	Injection sites include the thigh, upper arm, abdomen, or buttocks and should be rotated to avoid local irritation.
ZOMACTON	Vial, powder for reconstitution: 5 mg, 10 mg	Pediatric Growth hormone deficiency: 0.1 mg/kg SC three times a week	
ZORBTIVE	Vial, powder for reconstitution: 8.8 mg	SBS: 0.1 mg/kg SC daily to a maximum of 8 mg daily	Administration for more than 4 weeks has not been adequately studied. Treat moderate fluid retention and arthralgias symptomatically or reduce dose by 50%. Discontinue for up to 5 days for severe toxicities. Upon resolution of symptoms, resume at

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			50% of original dose. Permanently discontinue if severe toxicity recurs or does not disappear within 5 days. Injection sites should be rotated.

SPECIAL POPULATIONS

The precautions for use of somatropin in selected special populations are common for all formulations and are listed below in Table 4.

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
somatropin	Safety and efficacy in patients aged 65 years and older have not been established for somatropin. Elderly patients may be more sensitive to the actions of somatropin. A lower starting dose and smaller dose increments should be considered.	Safety and efficacy have not been established for ZORBTIVE and SEROSTIM.	Patients with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no formal studies have been conducted in patients with renal insufficiency.	A reduction in somatropin clearance has been noted in patients with hepatic dysfunction as compared with normal controls. However, no studies have been conducted in patients with hepatic impairment. The clinical significance of this decrease is unknown.	Pregnancy Category B: GENOTROPIN, OMNITROPE, SAIZEN, SEROSTIM, and ZORBTIVE Pregnancy Category C: HUMATROPE, NUTROPIN AQ, NORDITROPIN, and ZOMACTON Unknown whether excreted in breast milk; use with caution.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The safety and efficacy of GH therapy in pediatric patients with failure to grow is well established. Once a diagnosis of GHD is confirmed, GH therapy should be initiated immediately and continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 cm/year). Available GH preparations are indicated for use in a variety of pediatric conditions associated with a failure in growth, chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.
- The role of GH therapy in adult patients with GHD is less clear. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential

beneficial effects of GH therapy in adults are not as well established, including improvement in bone mineral density, sense of well-being, muscle strength and lipid profile (Molitch et al, 2011).

- There are several GH preparations currently available, which all contain somatropin (recombinant human growth hormone). The various preparations are equally biopotent and have the same natural sequence structure (Molitch et al, 2011). They vary primarily in the formulations and devices. All of the available GH preparations are available for SC injection and there are currently no generics available within the class.
- Adverse reactions that may be observed with GH therapy include fluid retention, hypoglycemia, hyperglycemia, hypothyroidism, hypertriglyceridemia, abnormal bone growth, carpal tunnel syndrome, and joint pain. Adverse effects seen with GH use in adults differ from those in children, particularly the incidence of peripheral edema and related side effects.
- Several delivery devices are available for administration of growth hormones. The dose frequency and dosing devices may be a factor in patient adherence with the prescribed regimen.
- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later, and short stature homeobox-containing gene deficiency (Bondy et al, 2007; Cohen et al, 2008; Deal et al, 2013; Goldstone et al, 2008; Grimberg et al, 2016; National Kidney Foundation, 2009). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utilized.
- For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD (Cook et al, 2009). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (Cook et al, 2009; Molitch et al, 2011). The 2009 American Association of Clinical Endocrinologists Guidelines state that no evidence exists to support any specific growth hormone product over another.

REFERENCES

- Abrahamsen B, Hangaard J, Horn HC, et al. Evaluation of the optimum dose of growth hormone (GH) for restoring bone mass in adult-onset GH deficiency: results from two 12-month randomized studies. Clin Endocrinol (Oxf). 2002 Aug;57(2):273-81.
- Abrahamsen B, Nielsen TL, Hangaard J, et al. Dose-, IGF-I- and sex-dependent changes in lipid profile and body composition during GH replacement therapy in adult onset GH deficiency. Eur J Endocrinol. 2004 May;150(5):671-9.
- Albertsson-Wikland K, Aronson AS, Gustafsson J, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. J Clin Endocrinol Metab. 2008 Nov;93(11):4342-50.
- Arends NJT, Boonstra VH, Mulder PGH, et al. GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: three-year results of a randomized, controlled GH trial. Clin Endocrinol (Oxf). 2003 Dec;59(3):779-87.
- Arwert LI, Deijen JB, Witlox J, Drent ML. The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: a meta-analysis. Growth Horm IGF Res. 2005 Feb;15(1):47-54.
- Arwert LI, Veltman DJ, Deijen JB, et al. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. Neuroendocrinology. 2006;83(1):12-9.
- Attanasio AF, Shavrikova E, Blum WF, et al. Continued growth hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. J Clin Endocrinol Metab. 2004 Oct;89(10):4857-62.
- Attanasio AF, Shavrikova EP, Blum WF, Shalet SM. Quality of life in childhood onset growth hormone-deficient patients in the transition phase from childhood to adulthood. J Clin Endocrinol Metab. 2005 Aug;90(8):4525-9.
- Bannink E, Djurhuus CB, Christensen T, et al. Adult height and health-related quality of life after growth hormone therapy in small for gestational age subjects. J Med Econ. 2010;13(2):221-7.
- Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. J Clin Endocrinol Metab. 2014;99:852-860.
- Baxter L, Byrant L, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with turner syndrome. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD003887. DOI:10.1002/14651858.CD00.887.pub2.
- Beauregard C, Utz AL, Schaub AE, et al. Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2008 Jun;93(6):2063-71.
- Bell W, Davies JS, Evans WD, et al. Somatic characteristics and cardiovascular risk factors in growth hormone deficiency: a randomized, double-blind, placebo-controlled study of the effect of treatment with recombinant human growth hormone. Am J Hum Biol. 2004 Sep-Oct;16(5):533-43.
- Bertrand AM, Chaussain JL, Job B, et al. Three years of GH treatment in Turner 's syndrome: complex effect of GH dosage on growth parameters. Clin Endocrinol (Oxf). 1996 Jun;44(6):665-71.
- Blum WF, Crowe BJ, Quigley CA, et al; SHOX Study Group. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: Two-year results of a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. 2007 Jan;92(1):219-28.

- Boguszewski M, Albertsson-Wikland K, Aronsson S, et al. Growth hormone treatment of short children born small-for-gestational-age: the Nordic Multicentre Trial. Acta Paediatr. 1998 Mar;87(3):257-63.
- Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007 Jan;92(1):10-25.
- Bozzola E, Lauriola S, Messina MF, et al. Effect of different growth hormone dosages on the growth velocity in children born small for gestational age. Horm Res. 2004;61(2):98-102.
- Bryant J, Baxter L, Cave CB, Milne R. Recombinant growth hormone for idiopathic short stature in children and adolescents. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004440.
- Burman P, Johansson AG, Siegbahn A, et al. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. J Clin Endocrinol Metab. 1997 Feb;82(2):550-5.
- Carrel AL, Myers SE, Whitman BY, et al. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in prader-willi syndrome: a controlled study. J Pediatr. 1999 Feb;132(2):215-21.
- Carrel AL, Moerchen V, Myers SE, et al. Growth hormone improves mobility and body composition in infants and toddlers with prader-willi syndrome. J Pediatr. 2004;145:744-9.
- Chatelain P, Job JC, Blanchard J, et al. Dose-dependent catch-up growth after two years of growth hormone treatment in intrauterine growth-retarded children. Belgian and French Pediatric Clinics and Sanofi-Choay (France). J Clin Endocrinol Metab. 1994 Jun;78(6):1454-60.
- Chihara K, Kato Y, Shimatsu A, et al. Efficacy and safety of individualized growth hormone treatment in adult Japanese patients with growth hormone deficiency. Growth Horm IGF Res. 2008[a] Oct;18(5):394-403.
- Chihara K, Kato Y, Kohno H, et al. Safety and efficacy of growth hormone (GH) during extended treatment of adult Japanese patients with GH deficiency (GHD). Growth Horm IGF Res. 2008[b] Aug;18(4):307-17.
- Chihara K, Kato Y, Kohno H, et al. Efficacy and safety of growth hormone (GH) in the treatment of adult Japanese patients with GH deficiency: a randomized, placebo-controlled study. Growth Horm IGF Res. 2006 Apr;16(2):132-42.
- Chihara K, Koledova E, Shimatsu A, et al. An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency. Eur J Endocrinol. 2005 Jul;153(1):57-65.
- Chihara K, Koledova E, Shimatsu A, et al. Adult GH deficiency in Japanese patients: effects of GH treatment in a randomized, placebo-controlled trial. Eur J Endocrinol. 2004 Sep;151(3):343-50.
- Chipman JJ, Attanasio AF, Birkett MA, et al. The safety profile of GH replacement therapy in adults. Clin Endocrinol (Oxf). 1997 Apr;46(4):473-81.
- Coelho R, Brook CG, Preece MA, et al. A randomized study of two doses of biosynthetic human growth hormone on final height of pubertal children with growth hormone deficiency. Horm Res. 2008;70(2):85-8.
- Cohen P, Bright GM, Rogol AD, et al; American Norditropin Clinical Trials Group. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. J Clin Endocrinol Metab. 2002 Jan;87(1):90-8.
- Cohen P, Rogol AD, Deal CL, et al; 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008 Nov;93(11):4210-7.
- Colao A, Di Somma C, Rota F, et al. Short-term effects of growth hormone (GH) treatment or deprivation on cardiovascular risk parameters and intima-media thickness at carotid arteries in patients with severe GH deficiency. J Clin Endocrinol Metab. 2005 Apr;90(4):2056-62.
- Conway GS, Szarras-Czapnik M, Racz K, et al; 1369 GHD to GHDA Transition Study Group. Treatment for 24 months with recombinant human GH has a beneficial effect on bone mineral density in young adults with childhood-onset GH deficiency. Eur J Endocrinol. 2009 Jun;160(6):899-907.
- Cook DM, Yuen KC, Biller BM, et al; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients - 2009 update. Endocr Pract. 2009 Sep-Oct;15(Suppl 2):1-29.
- Cuneo RC, Salomon F, Watts GF, et al. Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. Metabolism. 1993 Dec;42(12):1519-23.
- Davidson P, Milne R, Chase D, Cooper C. Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2004 Jan;60(1):92-8.
- de Muinck Keizer-Schrama SM, Rikken B, Wynne HJ, et al. Dose-response study of biosynthetic human growth hormone (GH) in GH-deficient children: effects on auxological and biochemical parameters. Dutch Growth Hormone Working Group. J Clin Endocrinol Metab. 1992 Apr;74(4):898-905.
- De Schepper J, Thomas M, Beckers D, et al. Growth hormone treatment and fat redistribution in children born small for gestational age. J Pediatr. 2008;152:327-30.
- de Zegher F, Hokken-Koelega A. Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. Pediatrics. 2005 Apr;115(4):e458-62.
- de Zegher F, Albertsson-Wikland K, Wilton P, et al. Growth hormone treatment of short children born small for gestational age: metanalysis of four independent, randomized, controlled, multicentre studies. Acta Paediatr Suppl. 1996 Oct;417:27-31.
- Deal CL, Tony M, Hyobye C, et al. Growth Hormone Research Society Workshop Summary: Consensus guidelines for recombinant human growth hormone therapy in Prader-Willi Syndrome. J Clin Endocrinol Metab. 2013;98:E1072-E1087.
- Drake WM, Carroll PV, Maher KT, et al. The effect of cessation of growth hormone (GH) therapy on bone mineral accretion in GH-deficient adolescents at the completion of linear growth. J Clin Endocrinol Metab. 2003 Apr;88(4):1658-63.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 1, 2017.
- Edén S, Wiklund O, Oscarsson J, et al. Growth hormone treatment of growth hormone-deficient adults results in a marked increase in Lp(a) and HDL cholesterol concentrations. Arterioscler Thromb. 1993 Feb;13(2):296-301.
- Elgzyri T, Castenfors J, Hägg E, et al. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly patients with GH deficiency. Clin Endocrinol (Oxf). 2004 Jul;61(1):113-22.
- Falleti MG, Maruff P, Burman P, Harris A. The effects of growth hormone (GH) deficiency and GH replacement on cognitive performance in adults: a meta-analysis of the current literature. Psychoneuroendocrinology. 2006 Jul;31(6):681-91.

- Festen DAM, de Lind van Wijngaarden R, van Eekelen M, et al. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. Clin Endocrinol (Oxf). 2008 Sep;69(3):443-51.
- Fine RN, Attie KM, Kuntze J, et al; Genentech Collaborative Study Group. Recombinant human growth hormone in infants and young children with chronic renal insufficiency. Pediatr Nephrol. 1995;9:451-7.
- Finkelstein BS, Imperiale TF, Speroff T, et al. Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. Arch Pediatr Adolesc Med. 2002 Mar;156(3):230-40.
- GENOTROPIN prescribing information. Pharmacia & Upjohn Co. New York, NY. December 2016.
- Gilchrist FJ, Murray RD, Shalet SM. The effect of long-term untreated growth hormone deficiency (GHD) and nine years of GH replacement on the quality of life (QoL) of GH-deficient adults. Clin Endocrinol (Oxf). 2002 Sep;57(3):363-70.
- Goldstone AP, Holland AJ, Hauffa BP, et al; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008 Nov;93(11):4183-97.
- Gómez JM, Gómez N, Fiter J, Soler J. Effects of long-term treatment with GH in the bone mineral density of adults with hypopituitarism and GH deficiency and after discontinuation of GH replacement. Horm Metab Res. 2000 Feb;32(2):66-70.
- Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Pediatr. 2016;86:361-397.
- Hartman ML, Xu R, Crowe BJ, et al. Prospective safety surveillance of gh-deficient adults: comparison of gh-treated vs untreated patients. J Clin Endocrinol Metab. 2013 March;98(3): 980–8.
- Hoffman AR, Kuntze JE, Baptista J, et al. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2004[a] May;89(5):2048-56.
- Hoffman AR, Strasburger CJ, Zagar A, et al. Efficacy and tolerability of an individualized dosing regimen for adult growth hormone replacement therapy in comparison with fixed body weight-based dosing. J Clin Endocrinol Metab. 2004[b] Jul;89(7):3224-33.
- Holmes SJ, Whitehouse RW, Swindell R, et al. Effect of growth hormone replacement on bone mass in adults with adult onset growth hormone deficiency. Clin Endocrinol (Oxf). 1995 Jun;42(6):627-33.
- Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. J Pediatr. 1993 Aug;123(2):215-22.
- HUMATROPE prescribing information. Eli Lily and Company. Indianapolis, IN. December 2016.
- Hwu CM, Kwok CF, Lai TY, et al. Growth hormone (GH) replacement reduces total body fat and normalizes insulin sensitivity in GH-deficient adults: a report of one-year clinical experience. J Clin Endocrinol Metab. 1997 Oct;82(10):3285-92.
- Janssen YJ, Hamdy NA, Frölich M, et al. Skeletal effects of two years of treatment with low physiological doses of recombinant human growth hormone (GH) in patients with adult-onset GH deficiency. J Clin Endocrinol Metab. 1998 Jun;83(6):2143-8.
- Jung H, Land C, Nicolay C, et al. Growth response to an individualized vs fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. Eur J Endocrinol. 2009 Feb;160(2):149-56.
- Kehely A, Bates PC, Frewer P, et al. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. J Clin Endocrinol Metab. 2002 May;87(5):1974-9.
- Kriström B, Aronson AS, Dahlgren J, et al. Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature. J Clin Endocrinol Metab. 2009 Feb;94(2):483-90.
- Leese GP, Wallymahmed M, VanHeyningen C, et al. HDL-cholesterol reductions associated with adult growth hormone replacement. Clin Endocrinol (Oxf). 1998 Nov;49(5):673-7.
- Lindgren AC, Hagenas L, Muller J, et al. Effects of growth hormone treatment on growth and body composition in prader-willi syndrome: a preliminary report. The Swedish National Growth Hormone Advisory Group. Acta Paediatr Suppl. 1997 Nov;423:60-2.
- Lindgren AC, Hagenas L, Muller J, et al. Growth hormone treatment of children with prader-willi syndrome affects linear growth and body composition favorably. Acta Paediatr. 1998;87:28-31.
- Lindgren AC, Ritzen EM; Swedish National Growth Hormone Advisory Group. Five years of growth hormone treatment in children with prader-willi syndrome. Acta Paediatr Suppl. 1999;433:109-11.
- MacGillivray MH, Baptista J, Johanson A. Outcome of a four-year randomized study of daily vs three times weekly somatropin treatment in prepubertal naive growth hormone-deficient children. Genentech Study Group. J Clin Endocrinol Metab. 1996 May;81(5):1806-9.
- Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. Pediatrics. 2009 Sep;124(3):e519-31.
- Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. Circulation. 2003 Nov 25;108(21):2648-52.
- Massa G, Otten BJ, de Muinck Keizer-Schrama SMPF, et al. Treatment with two growth hormone regimens in girls with turner syndrome: final height results. Horm Res. 1995;43:144-46.
- Mathioudakis N and Salvatori R. Adult-onset growth hormone deficiency: causes, complications and treatment options. Curr Opin Endocrinol Diabetes Obes 2008;15:352-358.
- Mauras N, Attie KM, Reiter EO, et al. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. J Clin Endocrinol Metab. 2000 Oct;85(10):3653-60.
- Mauras N, Pescovitz OH, Allada V, et al; Transition Study Group. Limited efficacy of growth hormone (GH) during transition of GH-deficient patients from adolescence to adulthood: a phase III multicenter, double-blind, randomized two-year trial. J Clin Endocrinol Metab. 2005 Jul;90(7):3946-55.
- Molitch ME, Clemmons DR, Malozowski S; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jun;96(6):1587-609.
- Moyle GJ, Daar ES, Gertner JM, et al; Serono 9037 Study Team. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2004 Apr 1;35(4):367-75.
- Myers SE, Carrel AL, Whitman BY, et al. Physical effects of growth hormone treatment in children with prader-willi syndrome. Acta Paediatr. 1999 (Suppl);433:112-4.

- Myers SE, Whitman BY, Carrel AL, et al. Two years of growth hormone therapy in young children with prader-willi syndrome. Am J Med Genet A. 2007 Mar 1;143(5):443-8.
- National Kidney Foundation. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Am J Kidney Dis. 2009 Mar;53(3 Suppl 2):S11-104.
- Newman CB, Frisch KA, Rosenzweig B, et al. Moderate doses of hGH (0.64 mg/d) improve lipids but not cardiovascular function in GH-deficient adults with normal baseline cardiac function. J Clin Endocrinol Metab. 2011 Jan;96(1):122-32.
- Nienhuis HE, Rongen-Westerlaken C, Wit JM, et al. Results of long-term therapy with growth hormone in two dose regimens in Turner Syndrome. Horm Res. 1993;39(Suppl 2):31-6.
- Nolte W, Rädisch C, Armstrong VW, et al. The effect of recombinant human GH replacement therapy on lipoprotein(a) and other lipid parameters in adults with acquired GH deficiency: results of a double-blind and placebo-controlled trial. Eur J Endocrinol. 1997 Nov;137(5):459-66.
- Noordam C, van der Burgt I, Sengers RCA, et al. Growth hormone treatment in children with Noonan's syndrome: four year results of a partly controlled trial. Acta Paediatr. 2001;90:889-94.
- NORDITROPIN prescribing information. Novo Nordisk Inc. Plainsboro, NJ. December 2016.
- NUTROPIN AQ prescribing information. Genentech, Inc. South San Francisco, CA. December 2016.
- OMNITROPE prescribing information. Sandoz Inc. Princeton, NJ. December 2016.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 1, 2017.
- PR Newswire. Ferring Pharmaceuticals receives FDA approval for growth hormone name change, acquires ZOMACTON™ [somatropin (rDNA origin)] for injection and needle-free device in the U.S. http://www.prnewswire.com/news-releases/ferring-pharmaceuticals-receives-fda-approval-for-growth-hormone-name-change-acquires-zomacton-somatropin-rdna-origin-for-injection-and-needle-free-device-in-the-us-300058056.html. Accessed March 1, 2017.
- Rahim A, Holmes SJ, Adams JE, et al. Long-term change in the bone mineral density of adults with adult onset growth hormone (GH) deficiency in response to short or long-term GH replacement therapy. Clin Endocrinol (Oxf). 1998 Apr;48(4):463-9.
- Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010;126(4):746-59.
- Romer T, Saenger P, Peter F, et al. Seven years of safety and efficacy of the recombinant human growth hormone Omnitrope in the treatment of growth hormone deficient children: results of a phase III study. Horm Res. 2009;72(6):359-69.
- Rosenfalck AM, Fisker S, Hilsted J, et al. The effect of the deterioration of insulin sensitivity on beta-cell function in growth-hormone-deficient adults following 4-month growth hormone replacement therapy. Growth Horm IGF Res. 1999 Apr;9(2):96-105.
- Rubeck KZ, Bertelsen S, Vestergaard P, et al. Impact of GH substitution on exercise capacity and muscle strength in GH-deficient adults: a meta-analysis of blinded, placebo-controlled trials. Clin Endocrinol (Oxf). 2009 Dec;71(6):860-6.
- Russell-Jones DL, Watts GF, Weissberger A, et al. The effect of growth hormone replacement on serum lipids, lipoproteins, apolipoproteins and cholesterol precursors in adult growth hormone deficient patients. Clin Endocrinol (Oxf). 1994 Sep;41(3):345-50.
- SAIZEN prescribing information. EMD Serono Inc. Rockland, MA. January 2017.
- Santos F, Moreno ML, Neto A, et al. Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. Clin J Am Soc Nephrol. 2010;5:1190-7.
- Sas TC, de Ridder MA, Wit JM, et al. Adult height in children with growth hormone deficiency: a randomized, controlled, growth hormone dose-response trial. Horm Res Paediatr. 2010;74(3):172-81.
- Sas TCJ, De Muinck Keizer-Schrama SMPF, Jansen M, et al. Normalization of height in girls with turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. J Clin Endocrinol Metab. 1999[a] Dec;84(12):4607-12.
- Sas T, de Waal W, Mulder P, et al. Growth hormone treatment in children with short stature born small for gestational age: five-year results of a randomized, double-blind, dose-response trial. J Clin Endocrinol Metab. 1999[b] Sep;84(9):3064-70.
- Schambelan M, Mulligan K, Grunfeld C, et al; Serostim Study Group. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Ann Intern Med. 1996 Dec 1;125(11):873-82.
- SEROSTIM prescribing information. EMD Serono Inc. Rockland MA. December 2016.
- Sesmilo G, Biller BM, Llevadot J, et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med. 2000 Jul 18;133(2):111-22.
- Shalet SM, Shavrikova E, Cromer M, et al. Effect of growth hormone (GH) treatment on bone in postpubertal GH-deficient patients: a 2-year randomized, controlled, dose-ranging study. J Clin Endocrinol Metab. 2003;88:4124-9.
- Shih KC, Ho LT, Kuo HF, et al. Linear growth response to recombinant human growth hormone in children with growth hormone deficiency. Zhonghua Yi Xue Za Zhi (Taipei). 1994 Jul;54(1):7-13.
- Sneppen SB, Hoeck HC, Kollerup G, et al. Bone mineral content and bone metabolism during physiological GH treatment in GH-deficient adults-an 18-month randomized, placebo-controlled, double blinded trial. Eur J Endocrinol. 2002 Feb;146(2):187-95.
- Snyder PJ, Biller BM, Zagar A, et al. Effect of growth hormone replacement on BMD in adult-onset growth hormone deficiency. J Bone Miner Res. 2007 May;22(5):762-70.
- Takano K, Shizume K, Hibi I. Turner's syndrome: treatment of 203 patients with recombinant human growth hormone for one year. A multicenter study. Acta Endocrinol (Copenh). 1989[a] May;120(5):559-68.
- Takano K, Shizume K, Hibi I; Committee for the Treatment of Turner's Syndrome. Endocrinol Japon. 1989[b];36(2):253-60.
- Takano K, Shizume K, Hibi I; Committee for the Treatment of Turner's syndrome. Endocrinol Japon. 1989[c];36(4):596-78.
- Takano K, Shizume K, Hibi I, Ogawa, Okada Y, Suwa S, et al. Growth hormone treatment in turner syndrome: results of a multicenter study in Japan. Horm Res. 1993;39(Suppl 2):37-41.
- Takano K, Shizume K, Hibi I, et al. Long-term effects of growth hormone treatment on height in turner syndrome: results of a six-year multicenter study in Japan. Horm Res. 1995;43:141-3.

- Underwood LE, Attie KM, Baptista J; Genentech Collaborative Study Group. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: a two-year, multicenter, multiple-dose, placebo-controlled study. J Clin Endocrinol Metab. 2003 Nov;88(11):5273-80.
- Vahl N, Juul A, Jørgensen JO, et al. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. J Clin Endocrinol Metab. 2000 May;85(5):1874-81.
- van Gool SA, Kamp GA, Odink RJ, et al. High-dose GH treatment limited to the prepubertal period in young children with idiopathic short stature does not increase adult height. Eur J Endocrinol. 2010 Apr;162(4):653-60.
- van Pareren YK, de Muinck Keizer-Schrama SMPF, Stijnen T, et al. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab. 2003 Mar;88(3):1119-25.
- Van Teunenbroek A, De Muinck Keizer-Schrama SMPF, Stijnen T, et al. Yearly stepwise increments of the growth hormone dose results in a better growth response after four years in girls with Turner Syndrome. J Clin Endocrinol Metab. 1996 Nov;81(11):4013-21.
- Verhelst J, Abs R, Vandeweghe M, et al. Two years of replacement therapy in adults with growth hormone deficiency. Clin Endocrinol (Oxf). 1997 Oct;47(4):485-94.
- Vimalachandra D, Hodson EM, Willis NS, et al. Growth hormone for children with chronic kidney disease. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD003264. DOI:10.1002/14651858.CD003264.pub2.
- Wales PW, Nasr A, de Silva N, and Yamada J. Human growth hormone and glutamine for patients with short bowel syndrome. The Cochrane Library. June 2010.
- Weaver JU, Monson JP, Noonan K, et al. The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab. 1995 Jan;80(1):153-9.
- Webster JM, Stewart M, al-Maskari M, et al. The effect of growth hormone replacement therapy for up to 12 months on lipoprotein composition and lipoprotein(a) in growth hormone-deficient adults. Atherosclerosis. 1997 Aug;133(1):115-21.
- Widdowson WM, Gibney J. The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. Clin Endocrinol (Oxf). 2010 Jun;72(6):787-92.
- Wilson DM, Baker B, Hintz RL, Rosenfeld RG. Subcutaneous vs intramuscular growth hormone therapy: growth and acute somatomedin response. Pediatrics. 1985 Sep;76(3):361-4.
- Wit JM, Rekers-Mombarg LT, Cutler GB, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr. 2005 Jan;146(1):45-53.
- Yuen KC, Frystyk J, White DK, et al. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. Clin Endocrinol (Oxf). 2005 Oct;63(4):428-36.
- ZOMACTON prescribing information. Ferring Pharmaceuticals, Inc. Parsippany, NJ. September 2016.
- ZORBTIVE prescribing information. EMD Serono, Inc. Rockland, MA. December 2016.

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Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2017, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2017*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective on complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When

combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2017*).

- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1). Of these agents, mephobarbital and ezogabine are not currently marketed as either brand or generic formulations, but are included in this review for informational and historical purposes.
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, and gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Mephobarbital* (Mebaral)‡	-‡
Pentobarbital (Nembutal†)	✔
Phenobarbital* (Luminal†, Solfotyn†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi)	-
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium§)	✔ ‖
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Ezogabine (Potiga)‡	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	- #
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Spritam)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	-
Rufinamide (Banzel)	- #
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid (Depacon, Depakene, Stavzor DR‡)	✔ ‖
Vigabatrin (Sabril)	-
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
‡ No brand or generic currently marketed
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
# Generic is FDA-approved for at least 1 strength or formulation, but not currently marketed
** Branded generic
†† Branded generic; not currently marketed

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	A*	✔ *			A		✔, A*	✔, A		✔ *	A*	✔, A*		A*	✔, A*	✔, A*	A*
Primary generalized tonic-clonic seizure (grand mal)		✔								✔			✔ *			A*	A*
Absence seizure (petit mal)				✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures							A										
Seizures of Lennox-Gastaut syndrome (LGS)			A*	✔, A								A*				A*	
Juvenile myoclonic epilepsy (JME)																	A*
Emergency/acute/short-term use for seizure control (see notes)						✔ *							✔ *				
Akinetic and myoclonic seizures				✔, A													
Convulsive disorders (see notes)						A*											
Certain mixed seizure patterns or other partial or generalized seizures		✔ *															

Indications	Brivaracetam	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Migraine prophylaxis							✔ *										
Trigeminal neuralgia		✔ *															
Postherpetic neuralgia														✔ *			
Bipolar disorder		✔ *					✔ *									✔	
Panic disorder, with or without agoraphobia				✔													
Anxiety disorder; short-term relief of anxiety symptoms					✔	✔											
Symptomatic relief of acute alcohol withdrawal					✔	✔											
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome						A											

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✔, A*		✔ *		✔ *	A*	✔, A*		A*	✔, A*	✔, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)	✔				A*		✔ *		✔, A*			✔, A*			
Absence seizure (petit mal)	✔	✔ *											✔, A*		
Multiple seizure types which include absence seizures													A*		
Seizures of LGS										A*		A*			
Emergency/acute/short-term use for seizure control (see notes)				✔ *			✔ *								
Infantile spasms														✔ *	
Convulsive disorders (see notes)						✔ *									
Migraine prophylaxis												✔ *	✔ *		
Postherpetic neuralgia								✔							
Bipolar disorder													✔ *		

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Sedative for anxiety, tension, and apprehension	✔														
Neuropathic pain associated with diabetic peripheral neuropathy								✔							
Neuropathic pain associated with spinal cord injury								✔							
Fibromyalgia								✔							

✓ = monotherapy (or not specified); A = adjunctive therapy
†Mephobarbital and phenobarbital are not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam**:
  - Adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 16 years of age with epilepsy
- **Carbamazepine**:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam**:
  - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam**:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam**:
  - Oral diazepam may be used adjunctively in convulsive disorders
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)
  - Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age ≥ 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
  - The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
    - Treatment of the manic episodes associated with bipolar disorder (tablets)
    - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)
- **Ethotoin**:

- Complex partial (psychomotor) seizures
- **Ezogabine**:
  - Adjunctive treatment of partial-onset seizures in patients ≥18 years of age who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity
- **Felbamate**:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin**:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin**:
  - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- **Lacosamide**:
  - In patients ≥ 17 years of age with partial-onset seizures as monotherapy or adjunctive therapy
- **Lamotrigine immediate-release formulations**:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets**:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam**:
  - Adjunctive therapy in the treatment of partial onset seizures in adults and children ≥ 1 month of age with epilepsy (age ≥ 4 years and weighing > 20 kg for the tablets for oral suspension [Spritam])
  - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years with JME
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 12 years of age with epilepsy
- **Methsuximide**:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- **Oxcarbazepine immediate-release formulations**:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets**:
  - Adjunctive therapy in the treatment of partial seizures in adults and children 6 to 17 years of age
- **Pentobarbital**:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel**:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 12

years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved)**:
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations**:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection**:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin**:
  - Adjunctive therapy for adult patients with partial onset seizures
- **Primidone**:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide**:
  - Adults and pediatric patients ≥ 1 year of age
- **Tiagabine**:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate**:
  - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- **Valproic acid**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
  - Migraine prophylaxis and bipolar disorder indications are for the delayed-release capsule formulation only (Stavzor, which is not currently marketed). For bipolar disorder:
    - Acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features; safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials
- **Vigabatrin**:
  - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
  - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide**:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, mephobarbital, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2017*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2017*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
    - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
    - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
  - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
    - Oxcarbazepine is potentially efficacious/effective.
    - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
  - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
    - Ethosuximide and valproate are established as efficacious/effective.
    - Lamotrigine is possibly efficacious/effective.
    - Gabapentin is established as inefficacious/ineffective.
    - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
  - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
    - Carbamazepine and valproate are possibly efficacious/effective.
    - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
  - For patients with newly diagnosed JME:
    - Topiramate and valproate are potentially efficacious/effective.

        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A recent Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures:
            - Levetiracetam performed better than carbamazepine and lamotrigine.
            - Lamotrigine performed better than all other treatments (aside from levetiracetam).
            - Carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital and phenytoin seem to perform better than most other drugs; and carbamazepine performed better than valproate, gabapentin, and lamotrigine.
        - For individuals with generalized seizures, phenytoin seems to work better than most other drugs.
        - There were few notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, levetiracetam, and zonisamide) for either partial seizures or generalized seizures.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2017*).
    - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A*).
    - This publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
    - Recommendations include the following:
        - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
        - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.

- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004B*).
  - This publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
    - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
    - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
    - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
    - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.

    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
    - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
    - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
  - Conclusions included the following (age not specified):
    - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
  - The overall treatment algorithm directs that:
    - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
    - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*). (Reaffirmed July 18, 2015)
  - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
  - Recommendations include the following:
    - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
    - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
    - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
    - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
    - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
    - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
  - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spams.

- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*). (Reaffirmed January 23, 2016)
  - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
  - Recommendations include the following:
    - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
    - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
  - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
  - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol (not available in the United States)
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
      - Dravet syndrome: topiramate, zonisamide, valproate
      - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
      - Provoked or situational seizures: carbamazepine
    - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and

Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
    - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
    - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
    - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
    - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
    - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
    - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
    - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
    - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
    - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
  - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
  - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
    - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
    - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.

    - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
    - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
  - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*).
  - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
  - American Psychiatric Society guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2016).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2017*).
- Common AEs among AEDs include the following (*Schachter 2017*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, abdominal pain, anorexia
    - rash, pruritus
    - hyponatremia (carbamazepine, oxcarbazepine)
    - weight gain (ezogabine, pregabalin, valproate), weight loss (felbamate, topiramate)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, behavioral changes, hyperactivity
    - attention disturbance, inattention
    - depression, mood alteration
    - confusion, memory impairment
    - ataxia, abnormal coordination, falls

    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2017*):
    - suicidal ideation and behavior (AEDs as a class)
    - neutropenia, leukopenia, pancytopenia, agranulocytosis, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, valproate, zonisamide)
    - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, phenobarbital, rufinamide, tiagabine, valproate, zonisamide)
    - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, primidone, phenobarbital, valproate)
    - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, ezogabine, lacosamide, rufinamide)
    - serum sickness (carbamazepine, ethosuximide, phenytoin, primidone, phenobarbital, valproate)
    - multiorgan hypersensitivity (gabapentin, lacosamide, lamotrigine, oxcarbazepine)
    - severe neuropsychiatric effects/hostility/aggression (perampanel)
    - vision loss (ezogabine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
    - Carbamazepine:
        - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
        - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
    - Clobazam, clonazepam, clorazepate, and diazepam:
        - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
    - Ezogabine:
        - Ezogabine can cause retinal and macular abnormalities and may be associated with vision loss. Ezogabine should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Ezogabine should be discontinued in patients who fail to show substantial clinical benefit after adequate titration. All patients taking ezogabine should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. If retinal pigmentary abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.
    - Felbamate:
        - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
        - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either AST or ALT become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
    - Fosphenytoin and phenytoin:

- There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.

- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment is recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*Vigabatrin REMS 2017*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Mephobarbital* (Mebaral)‡	tablets	oral	Once daily or divided 3 to 4 times per day	
Pentobarbital (Nembutal†)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal, Solfotyn)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Benzodiazepines				
Clobazam (Onfi)	tablets, oral suspension	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Tablet and capsule doses > 250 mg per day should be given in divided doses.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Ezogabine (Potiga)‡	tablets	oral	3 times per day	Tablets should be swallowed whole.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Spritam)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (*Lexicomp 2017*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Valproic acid (Depakene, Stavzor DR‡)	capsules, delayed-release capsules, oral solution/ syrup, injection	oral, IV	2 to 4 times per day (*Lexicomp 2017*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
‡ No brand or generic currently marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and it is often treated by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

REFERENCES

- Aptiom [package insert], Marlborough, MA: Sunovion Pharmaceuticals Inc.; September 2016.
- Banzel [package insert], Woodcliff Lake, NJ: Eisai Inc.; June 2015.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758-1765.
- Briviact [package insert], Smyrna, GA: UCB Inc.; February 2016.
- Carbatrol [package insert], Wayne, PA: Shire US Inc.; March 2013.
- Celontin [package insert], New York, NY: Pfizer Inc.; July 2010.
- Centers for Disease Control and Prevention (CDC). Epilepsy: Types of Seizures. CDC Web Site. https://www.cdc.gov/epilepsy/basics/types-of-seizures.htm. Updated April 10, 2017. Accessed July 24, 2017.
- Cerebyx [package insert], New York, NY: Pfizer Inc.; March 2017.
- Depacon [package insert], North Chicago, IL: AbbVie Inc.; May 2017.
- Depakene [package insert], North Chicago, IL: AbbVie Inc.; May 2017.
- Depakote (tablets) [package insert], North Chicago, IL: AbbVie Inc.; May 2017.
- Depakote ER [package insert], North Chicago, IL: AbbVie Inc.; May 2017.
- Depakote Sprinkle Capsules [package insert], North Chicago, IL: AbbVie Inc.; May 2017.
- Diastat & Diastat AcuDial [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; December 2016.
- Diazepam (injection) [package insert], Lake Forest, IL: Hospira Inc.; September 2016.
- Diazepam (oral solution) and Diazepam Intensol (oral concentrate) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; May 2016.
- Dilantin-125 (oral suspension) [package insert], New York, NY: Pfizer Inc.; November 2016.
- Dilantin (capsules) [package insert], New York, NY: Pfizer Inc.; December 2016.
- Dilantin Infatabs (chewable tablets) [package insert], New York, NY: Pfizer Inc.; December 2016.

- Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice Parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004; 63:959-965 (guideline reaffirmed February 8, 2008).
- Epilepsy Foundation. Lennox-Gastaut Syndrome. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. March 2014. Accessed July 24, 2017.
- Epilepsy Foundation. Seizure Types. Epilepsy Foundation Web site. https://epilepsychicago.org/epilepsy/seizure-types/generalized-seizures/. 2016. Accessed July 24, 2017.
- Epilepsy Foundation. Types of Epilepsy Syndromes. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. September 2013. Accessed July 24, 2017.
- Equetro [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; October 2016.
- Felbatol [package insert], Somerset, NJ: Meda Pharmaceuticals Inc.; August 2012.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
- Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017(A);58(4):531-542.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017(B);58(4):522-530.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(A);62:1252-1260.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(B);62:1261-1273.
- Fycompa [package insert], Woodcliff Lake, NJ: Eisai Inc.; April 2016.
- Gabitril [package insert], North Wales, PA: Teva Pharmaceuticals USA Inc.; August 2016.
- Glauser T, Ben-Menachem E, Bourgeois B, et al; for the ILAE subcommission of AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551-563.
- Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61.
- Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980 (guideline reaffirmed July 18, 2015).
- Gralise [package insert], Newark, CA: Depomed Inc.; December 2012.
- Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(A);73:133-141 (guideline reaffirmed July 13, 2013).
- Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(B);73:142-149 (guideline reaffirmed July 13, 2013).
- Hirschfeld RM, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder; second edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Originally published April 2002. Accessed July 23, 2017.
- Hirtz D, Berg A, Bettis D, et al. Practice Parameter: treatment of the child with a first unprovoked seizure. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60:166-175 (guideline reaffirmed January 23, 2016).
- Horizant [package insert], Atlanta, GA: Arbor Pharmaceuticals LLC; October 2016.
- Karceski S. Initial treatment of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated January 24, 2017. Accessed July 21, 2017.
- Keppra (injection) [package insert], Smyrna, GA: UCB Inc.; April 2017.
- Keppra (tablets & oral solution) [package insert], Smyrna, GA: UCB Inc.; April 2017.
- Keppra XR [package insert], Smyrna, GA: UCB Inc.; April 2017.
- Klonopin [package insert], South San Francisco, CA: Genentech Inc.; December 2016.
- Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705-1713.
- Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919-926.
- Lamictal (tablets, chewable dispersible tablets & orally disintegrating tablets) [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2016.
- Lamictal XR [package insert], Research Triangle Park, NC: GlaxoSmithKline; March 2016.
- LexiComp Web site. http://online.lexi.com/lco/action/home/switch. Accessed July 20, 2017.
- Lyrica [package insert], New York, NY: Pfizer Inc.; December 2016.
- Mebaral [package insert], Deerfield, IL: Lundbeck Inc.; May 2009 (archived label available at https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=25585). Accessed July 3, 2017.
- Mysoline [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; September 2012.
- Neurontin [package insert], New York, NY: Pfizer Inc.; March 2017.
- Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD011412. DOI: 10.1002/14651858.CD011412.pub2.
- Onfi [package insert], Deerfield, IL: Lundbeck Inc.; December 2016.

- Oxtellar XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; December 2015.
- Peganone [package insert], Lebanon, NJ: Recordati Rare Diseases; July 2016.
- Phenobarbital (elixir) [package insert], Huntsville, AL: Qualitest Pharmaceuticals; February 2015.
- Phenobarbital (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; June 2011.
- Phenobarbital (tablet) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; September 2015.
- Phenytoin (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; December 2016.
- Post RM. Bipolar disorder in adults: choosing maintenance treatment. UpToDate Web site. www.uptodate.com. Updated February 16, 2017. Accessed July 23, 2017.
- Potiga [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2016.
- Qudexy XR [package insert], Maple Grove, MN: Upsher-Smith Laboratories Inc.; March 2017.
- Sabril [package insert], Deerfield, IL: Lundbeck Inc.; April 2017.
- Schachter SC. Overview of the management of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated July 3, 2017. Accessed July 21, 2017.
- Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345 (guideline reaffirmed July 18, 2015).
- Sirven JI. Evaluation and management of drug-resistant epilepsy. UpToDate Web site. www.uptodate.com. Updated May 30, 2017. Accessed July 23, 2017.
- Spritam [package insert], East Windsor, NJ: Aprecia Pharmaceuticals Company; June 2017.
- Stavzor [package insert], Miami, FL: Noven Therapeutics LLC; August 2014.
- Stovall J. Bipolar disorder in adults: pharmacotherapy for acute mania and hypomania. UpToDate Web site. www.uptodate.com. Updated May 17, 2016. Accessed July 23, 2017.
- Tegretol and Tegretol-XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corp.; April 2017.
- Topamax [package insert], Titusville, NJ: Janssen Pharmaceuticals Inc.; June 2017.
- Tranxene T-TAB [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; September 2016.
- Trokendi XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; April 2017.
- Trileptal [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2017.
- Valium [package insert], South San Francisco, CA: Genentech Inc.; December 2016.
- Vigabatrin risk evaluation and mitigation strategy (REMS) document. Food and Drug Administration Web site. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Vigabatrin_2017-05-24_REMS_document.pdf. Updated May 2017. Accessed July 21, 2017.
- Vimpat [package insert], Smyrna, GA: UCB Inc.; March 2017.
- Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015;56(8):1185-1197.
- World Health Organization. Guidelines on neonatal seizures. World Health Organization Web site. http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/. 2011. Accessed July 25, 2017.
- Zarontin (capsules) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zarontin (oral solution) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zonegran [package insert], St. Michael, Barbados: Concordia Pharmaceuticals Inc.; April 2016.

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Therapeutic Class Overview
Ophthalmic Antibiotic Steroid Combinations

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with the symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms including *Staphylococcus* species, *Corynebacterium* species, and *Propionibacterium acnes*. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (American Academy of Ophthalmology [AAO], 2013[b]).
- Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. This infection rarely causes permanent visual loss or structural damage, and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (AAO, 2013[c]; American Optometric Association [AOA], 2002).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain, and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (AAO, 2013[c]; AOA, 2002).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea (Tauber et al, 2011). Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In addition, broad-spectrum ophthalmic antibiotics are used initially as empiric treatment. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (AAO, 2013[a]).
- Though not Food and Drug Administration-approved, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (AAO, 2016; AAO, 2013[d]; AOA, 2004).
- Ophthalmic antibiotic and steroid combinations are included in this review. Poly-Pred (neomycin/polymyxin/prednisolone) was discontinued by Allergan in 2011, and a generic product is not available (Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017). However, other polymyxin/neomycin products are available with another corticosteroid.
- Medispan class: Ophthalmic Steroid Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
bacitracin/neomycin/polymyxin/hydrocortisone	✔
Blephamide* (sulfacetamide/prednisolone)	✔ (solution only)
Maxitrol (neomycin/polymyxin/dexamethasone)	✔
neomycin/polymyxin/hydrocortisone	✔
Pred-G (gentamicin/prednisolone)	-

Drug	Generic Availability
Tobradex, Tobradex ST (tobramycin/dexamethasone)	✔ (suspension only)
Zylet (tobramycin/loteprednol)	-

*Blephamide is available as suspension and ointment; solution is only available as a generic.
(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

- Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns; or penetration of foreign bodies.

Indication	bacitracin/neomycin/polymyxin/hydrocortisone	Blephamide (sulfacetamide/prednisolone)	Maxitrol (neomycin/polymyxin/dexamethasone)	neomycin/polymyxin/hydrocortisone	Pred-G (gentamicin/prednisolone)	Tobradex, Tobradex ST (tobramycin/dexamethasone)	Zylet (tobramycin/loteprednol)
Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exists.	✔	✔	✔	✔	✔	✔	✔

(Prescribing information: bacitracin/neomycin/polymyxin/hydrocortisone, 2011; BLEPHAMIDE ointment, 2014; BLEPHAMIDE, suspension 2014; MAXITROL suspension, 2017; MAXITROL ointment, 2017; neomycin/polymyxin/hydrocortisone, 2011; PRED-G ointment, 2017; PRED-G suspension, 2017; sulfacetamide/prednisolone solution, 2013; TOBRADEX ointment, 2010; TOBRADEX suspension, 2015; TOBRADEX ST, 2011; ZYLET, 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that ophthalmic antibiotic steroid combination products are effective in treating patients with external ocular infections, including bacterial blepharitis, conjunctivitis, and blepharokeratoconjunctivitis (Rhee et al, 2007; Shulman et al, 1996; White et al, 2008).
- In one study involving patients with moderate blepharokeratoconjunctivitis, reductions in blepharitis and conjunctivitis symptom scores were greater with ophthalmic tobramycin/dexamethasone therapy compared to ophthalmic tobramycin/loteprednol therapy, while the reductions in keratitis symptom scores were similar between the two treatment groups (Rhee et al, 2007).
- In another study, the reduction in composite symptom scores in patients with blepharokeratoconjunctivitis was similar between the tobramycin/dexamethasone and tobramycin/loteprednol groups; however, the increase in intraocular pressure was significantly greater with tobramycin/dexamethasone than tobramycin/loteprednol (White et al, 2008).
- Another study involving patients with moderate to severe acute blepharitis/blepharoconjunctivitis showed initial therapy with the combination of tobramycin/dexamethasone ST provides faster inflammation relief than azithromycin ophthalmic based on a statistically significant lower mean global score (p = 0.0002) (Torkildsen et al, 2011).

- One study showed that when compared to dexamethasone alone, neomycin/polymyxin B/dexamethasone resulted in significantly greater bacterial eradication and decrease in bacterial count in patients with bacterial blepharitis or conjunctivitis; however, the reduction in signs and symptoms of ocular infection was similar between the two treatment groups (Shulman et al, 1996).
- In patients undergoing cataract and posterior chamber lens implant surgery, treatment with ophthalmic gentamicin resulted in lower bacterial colony count compared to ophthalmic neomycin/polymyxin B/dexamethasone at days 6 and 8 ($p = 0.033$); however, there was no significant difference between the two groups with regard to the degree of intraocular inflammation or the global assessment of the success of therapy and local tolerance (p value not reported) (Van Endt et al, 1997). In a separate study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14 and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 ($p < 0.05$ for all), and scores in the ophthalmic neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 ($p < 0.05$) (Notivol et al, 2004).

CLINICAL GUIDELINES

- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin and note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (AAO, 2013[b]).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with cefazolin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones (AAO, 2013[a]).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment (AAO, 2013[b]; AOA, 2002).
- Short-term use of ophthalmic corticosteroids is recommended by treatment guidelines to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis, and can be considered in postoperative prophylaxis (AAO, 2016; AAO, 2013[a]; AAO, 2013[b]; AAO, 2013[c]).

SAFETY SUMMARY

- Prolonged use of corticosteroids may result in the following: Development of glaucoma, corneal or scleral thinning which can lead to perforation, suppression of host response causing secondary infection, and/or purulent infections of the eye may be masked or activity enhanced.
- If using these products for longer than 10 days, monitor intraocular pressure (IOP). Use after cataract surgery may delay healing. Overgrowth of nonsusceptible organisms including fungi may occur.
- Blephamide (sulfacetamide/prednisolone) may cause acute anterior uveitis in susceptible individuals, primarily Blacks. The p-aminobenzoic acid present in purulent exudates competes with sulfonamides and can reduce their effectiveness.
- Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitization reactions including itching, swelling and conjunctival erythema. The reactions due to the corticosteroid component are elevation of IOP with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
bacitracin/ neomycin/ polymyxin/	ophthalmic ointment: bacitracin zinc 400 units/neomycin sulfate	Apply to the affected eye(s) every 3 or 4 hours, depending on the severity of	Not more than 8 grams should be prescribed initially.

Drug	Available Formulations	Usual Recommended Frequency	Comments
hydrocortisone	3.5 mg/ polymyxin B sulfate 10,000 units/ hydrocortisone 10 mg/gram	the condition.	
Blephamide (sulfacetamide/ prednisolone)	ophthalmic ointment: sulfacetamide 10%/ prednisolone 0.2% ophthalmic solution: sulfacetamide 10%/ prednisolone sodium 0.23% ophthalmic suspension: sulfacetamide 10%/ prednisolone 0.2%	**Ointment** Apply ½ inch ribbon to the conjunctival sac(s) 3 or 4 times daily and once or twice at night. **Solution** Instill 2 drops into the eye(s) every 4 hours. **Suspension** Instill 2 drops into the conjunctival sac(s) every 4 hours during the day and at bedtime.	Ointment: Not more than 8 grams should be prescribed initially. Solution and suspension: Not more than 20 mL should be prescribed initially.
Maxitrol (neomycin/ polymyxin/ dexamethasone)	ophthalmic ointment: neomycin 3.5 mg/ polymyxin B sulfate 10,000 units/ dexamethasone 0.1% per gram ophthalmic suspension: neomycin 3.5 mg/ polymyxin B sulfate 10,000 units/ dexamethasone 0.1% per mL	**Ointment** Apply a small amount into the conjunctival sac(s) up to 3 or 4 times daily. **Suspension** *Mild disease:* One to 2 drops in the conjunctival sac(s) up to 4 to 6 times daily. *Severe disease*: Drops may be used hourly, being tapered to discontinuation as the inflammation subsides.	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.
neomycin/ polymyxin/ hydrocortisone	ophthalmic suspension: neomycin sulfate 3.5 mg/polymyxin B sulfate 10,000 units/hydrocortisone10 mg/mL	Instill one or two drops into the affected eye(s) every 3 to 4 hours depending on the severity of the infection.	Not more than 20 mL should be prescribed initially.
Pred-G (gentamicin/ prednisolone)	ophthalmic ointment: gentamicin 0.3%/ prednisolone acetate 0.6% ophthalmic suspension: gentamicin 0.3%/ prednisolone acetate 1%	**Ointment** Apply ½ inch ribbon in the conjunctival sac(s) 1 to 3 times daily. **Suspension** Instill 1 drop into the conjunctival sac(s) 2 to 4 times daily. During the initial 24 to 48 hours, the dosing may be increased up to 1 drop every hour.	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.
Tobradex,	ophthalmic ointment:	**Ointment**	Ointment: Not more than 8 grams

Drug	Available Formulations	Usual Recommended Frequency	Comments
Tobradex ST (tobramycin/ dexamethasone)	tobramycin 0.3%/ dexamethasone 0.1% ophthalmic suspension: tobramycin 0.3%/ dexamethasone 0.1% ophthalmic ST suspension: tobramycin 0.3%/ dexamethasone 0.05%	Apply ½ inch ribbon into the conjunctival sac(s) up to 3 or 4 times daily. **Suspension** Instill 1 or 2 drops into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosage may be increased to 1 or 2 drops every 2 hours. **ST Suspension** Instill 1 drop into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosage may be increased to 1 drop every 2 hours.	should be prescribed initially. Suspension, ST Suspension: Not more than 20 mL should be prescribed initially.
Zylet (tobramycin/ loteprednol)	ophthalmic suspension: tobramycin 0.3%/ loteprednol etabonate 0.5%	Instill 1 or 2 drops into the conjunctival sac(s) every 4 to 6 hours. During the initial 24 to 48 hours, the dosing may be increased, to every 1 to 2 hours.	Not more than 20 mL should be prescribed initially.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotic steroid combination products are indicated for the treatment of steroid-responsive ocular inflammatory conditions where the presence or risk of a superficial bacterial ocular infection exists. At least one generic is available in each formulation: ointment, solution, and suspension.
- In comparative clinical trials, no one ophthalmic antibiotic steroid combination product has been shown to be more effective than another with regard to symptom improvement or reduction of postoperative inflammation.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotic steroid combinations are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should a super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated. Steroid-containing ophthalmic products may also increase the risk of intraocular pressure elevation, cataract formation, and delayed healing after cataract surgeries, and should be used with caution.
- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin and note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (AAO, 2013[b]).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with cefazolin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones (AAO, 2013[a]).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment (AAO, 2013[c], AOA, 2002).

- Short-term use of ophthalmic corticosteroids is recommended by treatment guidelines to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis and can be considered in postoperative prophylaxis (AAO, 2016; AAO, 2013[a]; AAO, 2013[b]; AAO, 2013[c]).

REFERENCES

- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Bacterial keratitis [guideline on the Internet]. San Francisco, CA: American Academy of Ophthalmology; 2013[a]. Available at: http://www.aao.org/preferred-practice-pattern/bacterial-keratitis-ppp--2013. Accessed June 5, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Blepharitis [guideline on the Internet]. San Francisco, CA: American Academy of Ophthalmology; 2013[b]. Available from: http://www.aao.org/preferred-practice-pattern/blepharitis-ppp--2013. Accessed June 5, 2017.
- American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Conjunctivitis [guideline on the Internet]. San Francisco, CA: American Academy of Ophthalmology; 2013[c]. Available from: http://www.aao.org/preferred-practice-pattern/conjunctivitis-ppp--2013. Accessed June 5, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Refractive errors and refractive surgery [guideline on the Internet]. San Francisco, CA: American Academy of Ophthalmology; 2013[d]. Available from: http://www.aao.org/preferred-practice-pattern/refractive-errors--surgery-ppp-2013 Accessed June 5, 2017.
- American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Cataract in the adult eye [guideline on the Internet]. San Francisco, CA: American Academy of Ophthalmology; 2016. Available from: https://www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp-in-press. Accessed June 5, 2017.
- American Optometric Association Consensus Panel on Care of the Adult Patient with Cataract. Care of the adult patient with cataract [guideline on the Internet]. St. Louis, MO: American Optometric Association; 2004 Mar. Available from: http://www.aoa.org/documents/CPG-8.pdf. Accessed November 30, 2016.
- American Optometric Association. Optometric Clinical Practice Guideline. Care of the patient with conjunctivitis [guideline on the internet]. 2002; Reviewed in 2007. St. Louis, MO: American Optometric Association; Available at: http://www.aoa.org/documents/optometrists/CPG-11.pdf. Accessed June 5, 2017.
- Bacitracin/neomycin/polymyxin/hydrocortisone prescribing information. Akorn, Inc. Lake Forest, IL. October 2011.
- Blephamide ophthalmic ointment prescribing information. Allergan, Inc. Irvine, CA. March 2014.
- Blephamide ophthalmic suspension prescribing information. Allergan, Inc. Irvine, CA. April 2014.
- Clinical Pharmacology [database on the Internet]. Tampa, FL: Elsevier/Gold Standard; Updated periodically. Available from: http://www.clinicalpharmacology.com/. Accessed June 5, 2017.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 5, 2017.
- Maxitrol ophthalmic suspension prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. April 2017..
- Maxitrol ophthalmic ointment prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. April 2017.
- Neomycin/polymyxin/hydrocortisone prescribing information. Falcon Pharmaceuticals, Ltd. Fort Worth, TX. August 2011.
- Notivol R, Bertin D, Amin D, et al. Comparison of topical tobramycin-dexamethasone with dexamethasone-neomycin-polymyxin and neomycin-polymyxin-gramicidin for control of inflammation after cataract surgery: results of a multicenter; prospective, three-arm, randomized, double-masked, controlled, parallel-group study. Clin Ther. 2004 Aug;26(8):1274-85.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 5, 2017.
- Pred-G ophthalmic ointment prescribing information. Allergan, Inc. Irvine, CA. March 2017.
- Pred-G ophthalmic suspension prescribing information. Allergan, Inc. Irvine, CA. March 2017.
- Rhee SS, Mah FS. Comparison of tobramycin 03%/dexamethasone 0.1% and tobramycin 0.3%/loteprednol 0.5% in the management of blepharo-keratoconjunctivitis. Adv Ther. 2007 Jan-Feb;24(1):60-7.
- Shulman DG, Sargent JB, Stewart RH, et al. Comparative evaluation of the short-term bactericidal potential of a steroid-antibiotic combination vs steroid in the treatment of chronic bacterial blepharitis and conjunctivitis [abstract]. Eur J Ophthalmol. 1996;6(4):361-7.
- Sulfacetamide/prednisolone ophthalmic solution. Bausch & Lomb, Incorporated. Tampa, FL. January 2013.
- Tauber S, Cupp G, Garber R, et al. Microbiological efficacy of a new ophthalmic formulation of moxifloxacin dosed twice-daily for bacterial conjunctivitis. Adv Ther. 2011 Jul;28(7):566-74.
- Tobradex ophthalmic ointment prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. April 2010.
- Tobradex ophthalmic suspension prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. October 2015.
- Tobradex ST prescribing information. Alcon Laboratories, Inc. Fort Worth, TX. July 2011.
- Torkildsen GL, Cockrum P, Meier E, et al. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. Curr Med Res Opin. 2011; 27:171–78.

- Van Endt JJ, Veraart HG, Kramer R, et al. A comparison of two ophthalmic steroid-antibiotic combinations after cataract surgery [abstract]. Eur J Ophthalmol. 1997 Apr-Jun;7(2):144-8.
- White EM, Macy JI, Bateman KM, et al. Comparison of the safety and efficacy of loteprednol 0.5%/tobramycin 0.3% with dexamethasone 0.1%/tobramycin 0.3% in the treatment of blepharokeratoconjunctivitis. Curr Med Res Opin. 2008;24(1):287-96.
- Zylet prescribing information. Bausch & Lomb, Incorporated. Tampa, FL. August 2016.

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Therapeutic Class Overview
Anxiolytics, Sedatives and Hypnotics

INTRODUCTION

- Generalized anxiety disorder (GAD) is a common form of anxiety disorder characterized by excessive and uncontrollable worry that may manifest itself in a number of psychic and somatic symptoms such as irritability, difficulty concentrating, muscle tension, sweating, and nausea. To meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria, worry and other associated symptoms must be present more days than not for at least 6 months and must adversely affect the patient's life (*Baldwin et al 2017, DSM-V criteria*).
  - According to the National Institutes of Mental Health (NIMH), the 12-month prevalence of GAD is 3.1% in the United States (US) population *(NIMH Web site).*
  - The onset of GAD is usually before the age of 25 and is twice as common in females as males *(Baldwin et al 2017, World Health Organization [WHO] Web site).*
- Social anxiety disorder (SAD) is characterized by persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with social anxiety disorder often avoid social interactions or endure them with intense anxiety or distress *(Bandelow et al 2012).*
- Panic disorder is a form of anxiety disorder that is characterized by episodic, unexpected panic attacks that occur without a clear trigger. Panic attacks are defined by the rapid onset of intense fear (typically peaking within about 10 minutes) with at least 4 of the physical and psychological symptoms listed in the DSM-V diagnostic criteria (ie, palpitations, sweating, trembling/shaking, sensations of shortness of breath, feelings of choking, chest pain/discomfort, nausea, feeling dizzy or unsteady, chills or heat sensations, paresthesias, derealization, fear of losing control, fear of dying) *(Locke et al 2015).*
- Effective treatments for GAD include cognitive-behavioral therapy and medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) *(Baldwin et al 2017).* Other agents, such as buspirone and hydroxyzine are also recommended as treatment options in clinical guidelines. The medication choice should be made based on several factors, such as efficacy, possible adverse events (AEs), contraindications, and drug interactions *(Bandelow et al 2015).*
  - Benzodiazepines (BZDs) have been widely used in managing GAD because of their rapid onset of action and proven efficacy. They can be helpful as short-term treatment during the period before antidepressants take effect and to help alleviate the restlessness and agitation that can occur with initiation of antidepressant therapy. All of the BZDs are considered to be of equal efficacy for the treatment of GAD *(Gliatto 2000).*
    - BZDs exert their effects through their activity at the gamma-aminobutyric acid type A (GABA) receptors, potentiating the effects of endogenous GABA, the main inhibitory neurotransmitter.
- Insomnia is defined as a complaint of trouble initiating or maintaining sleep which is associated with day time consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep *(Sateia et al 2017)*.
  - Insomnia is considered chronic when it has persisted for at least 3 months at a frequency of at least 3 times per week. The prevalence of chronic insomnia in industrialized nations is estimated to be at least 5% to 10%.
  - Insomnia is considered short-term when the disorder meets symptom criteria but has persisted for less than 3 months. Occasional, short-term insomnia is thought to affect 30% to 50% of the population.
- Insomnia often occurs with comorbid disorders, including depression, anxiety, and substance abuse *(Schutte-Rodin et al 2008)*.
  - Certain medical or psychiatric disorders may also increase the risk of insomnia; psychiatric and chronic pain disorders have been associated with insomnia in as many as 50 to 75% of patients.
  - Insomnia is also associated with an increased risk of suicide and may result in relapse among prior substance abusers.
- The primary treatment goals are to improve sleep quality and quantity and to improve insomnia-related daytime impairments *(Schutte-Rodin et al 2008)*.

- General treatment measures for insomnia include the treatment of comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimizing the sleep environment. Part of the initial approach to treatment should include cognitive behavioral therapy (*Sateia et al 2017, Schutte-Rodin et al 2008)*.
- Prior to the introduction of BZDs, barbiturates and related compounds were commonly used for the management of anxiety and sleep disturbance. The first BZD, chlordiazepoxide, was introduced to the US market in 1963, followed shortly by diazepam. Flurazepam, the first BZD approved as a hypnotic, became available in 1970 and rapidly supplanted the use of barbiturates and other related compounds for the treatment of insomnia. Zolpidem, the first non-BZD hypnotic approved in the US, became available in 1992 and remains the most widely prescribed hypnotic medication *(Sateia et al 2017)*.
- Other than zolpidem, the non-BZD sedative hypnotics used to treat insomnia are doxepin (Silenor), eszopiclone (Lunesta), ramelteon (Rozerem), suvorexant (Belsomra), tasimelteon (Hetlioz), and zaleplon (Sonata).
  - Ramelteon and tasimelteon are melatonin receptor agonists that possess affinity for the MT1 and MT2 receptors vs. the MT3 receptor. Tasimelteon has a unique indication for treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), a circadian rhythm sleep disorder found predominantly in the blind and characterized by excessive sleepiness during the day and an inability to sleep at night.
  - Doxepin's mechanism of action is not fully understood, but it is thought that antagonism of the H1 receptor is the most likely mechanism by which doxepin exerts it sleep maintenance effect.
  - The remaining agents act at the GABA-receptor.
- All of the agents in this review (with the exception of tasimelteon) have been shown to result in positive effects on sleep latency, total sleep time (TST) and/or wake time after sleep onset (WASO). The BZDs have been shown to be effective in improving sleep latency and TST. Other agents such as zaleplon and ramelteon are effective in reducing sleep latency, whereas medications such as eszopiclone and temazepam are more likely to improve sleep maintenance *(Schutte-Rodin et al 2008)*.
- Although a substantial number of Food and Drug Administration (FDA)- and non FDA-approved anxiolytics and sedative hypnotics are available, the focus of this review will be on BZDs and non-BZDs agents. Other classes of agents such as barbiturates, SNRIs, SSRIs, and tricyclic antidepressants (TCAs) are also utilized in these settings, but will not be the focus of this review.
- Several BZDs have additional FDA-approved indications such as alcohol withdrawal, seizure disorder, and muscle relaxation. These indications are outside the scope of this review, and therefore will not be addressed in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Benzodiazepines	
Xanax (alprazolam)	✔
chlordiazepoxide	✔ §
Klonopin (clonazepam)	✔
Tranxene-T (clorazepate)	✔
Valium (diazepam)	✔
estazolam	✔ §
flurazepam	✔ §
Ativan (lorazepam)	✔
oxazepam	✔ §
Restoril (temazepam)	✔
Halcion (triazolam)	✔
Doral (quazepam)	✔
Non-benzodiazepines	
buspirone	✔ §
Silenor (doxepin)	-
Lunesta (eszopiclone)	✔
meprobamate	✔

Drug	Generic Availability
Rozerem (ramelteon)	-
Belsomra (suvorexant)	-
Hetlioz (tasimelteon)	-
Sonata (zaleplon)	✔
Ambien, Edluar, Intermezzo, Zolpimist (zolpidem) Ambien CR (zolpidem extended-release)	✔ *

*Edluar and Zolpimist are not available as generics
§ Buspar (buspirone) Dalmane (flurazepam), Librium (chlordiazepoxide), Prosom (estazolam), and Serax (oxazepam) are brands that are no longer marketed

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	BZDs													Non-BZDs							
Indication	**alprazolam**	**chlordiazepoxide**	**clonazepam**	**clorazepate**	**diazepam**	**estazolam**	**flurazepam**	**lorazepam**	**oxazepam**	**temazepam**	**triazolam**	**quazepam**	**buspirone**	**doxepin**	**eszopiclone**	**meprobamate**	**ramelteon**	**suvorexant**	**tasimelteon**	**zaleplon**	**zolpidem**
Short term treatment of insomnia characterized by difficulties with sleep initiation/onset																	✔				✔ (Ambien, Ambien CR, Edluar, Zolpimist)
Treatment of insomnia, characterized by difficulties with sleep maintenance														✔							
Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance																		✔			
Treatment of insomnia characterized						✔ (short-term use)	✔					✔									

	BZDs													Non-BZDs							
Indication	**alprazolam**	**chlordiazepoxide**	**clonazepam**	**clorazepate**	**diazepam**	**estazolam**	**flurazepam**	**lorazepam**	**oxazepam**	**temazepam**	**triazolam**	**quazepam**	**buspirone**	**doxepin**	**eszopiclone**	**meprobamate**	**ramelteon**	**suvorexant**	**tasimelteon**	**zaleplon**	**zolpidem**
by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings																					
Short-term treatment of insomnia										✔	✔									✔	
Treatment of insomnia															✔						
Treatment of non-24-hour sleep-wake disorder																			✔		
As needed treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep																					✔ (Intermezzo)
Management of anxiety disorder or short-term relief of symptoms of anxiety	✔	✔		✔	✔			✔	✔				✔			✔					
Treatment of panic disorder, with or without agoraphobia	✔		✔																		
Preoperative apprehension and anxiety		✔																			

	BZDs													Non-BZDs							
Indication	**alprazolam**	**chlordiazepoxide**	**clonazepam**	**clorazepate**	**diazepam**	**estazolam**	**flurazepam**	**lorazepam**	**oxazepam**	**temazepam**	**triazolam**	**quazepam**	**buspirone**	**doxepin**	**eszopiclone**	**meprobamate**	**ramelteon**	**suvorexant**	**tasimelteon**	**zaleplon**	**zolpidem**
Pre-anesthesia to produce sedation, relief of anxiety, and decreased ability to recall events related to surgery								✔													

(*Prescribing information: Ambien 2017, Ambien CR 2016, Belsomra 2016, buspirone 2016, chlordiazepoxide 2005, clonazepam 2008, diazepam 2014, Doral 2016, Edluar 2014, estazolam 2014, flurazepam 2013, Halcion 2016, Hetlioz 2014, Intermezzo 2015, lorazepam 2015, Lunesta 2014, meprobamate 2016, oxazepam 2017, Restoril 2016, Rozerem 2010, Silenor 2010, Sonata 2013, Tranxene-T 2016, Xanax 2017, Zolpimist 2016)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A meta-analysis that examined 105 randomized, double-blind (DB), placebo-controlled (PC) trials was conducted to evaluate safety and efficacy of drug treatments for chronic insomnia in adults. Of these trials, 52 involved BZDs, 48 involved non-BZDs, and 8 involved antidepressants (ADPs). Most of the studies had short-treatment duration (≤ 4 weeks) in the non-elderly population. The primary efficacy measure was sleep onset latency, with WASO as the secondary outcome measure (*Buscemi et al 2007)*.
  - Sleep onset latency was significantly decreased, as compared to placebo, when measured by polysomnography (PSG) for the BZDs (weighted mean difference [WMD]: −10.0 minutes; 95% confidence interval [CI], −16.6 to −3.4), non-BZDs (WMD −12.8 minutes; 95% CI, −16.9 to −8.8) and ADPs (WMD −7.0 minutes; 95% CI, −10.7 to −3.3) as well as when measured by sleep diary (WMD −19.6 minutes; 95% CI, −23.9 to −15.3; WMD −17.0 minutes; 95% CI,−20.0 to −14.0; WMD: −12.2 minutes; 95% CI, −22.3 to −2.2, respectively).
  - WASO, sleep efficiency, TST, and sleep quality were evaluated and subcategorized by PSG and sleep diary. All results were statistically significant and favored BZDs and non-BZDs except for the PSG studies measuring WASO and TST, which were just below the range of significance. The PSG results significantly favored the antidepressants, and the sleep diary results, which were fewer, favored the antidepressants for WASO. Placebo was favored for TST, however, the results did not achieve statistical significance.
  - All treatment groups had a statistically significant incidence of AEs compared to placebo (BZDs risk difference [RD]: 0.15; non-BZDs RD: 0.07; and antidepressants RD: 0.09), although the most commonly reported AEs were considered minor. The most common AEs reported in the BZD group were headache, somnolence, dizziness, nausea, and fatigue while the most common AEs in the non-BZD and ADP groups were headache, dizziness, nausea, and somnolence. Indirect comparisons suggest that BZDs and non-BZDs have similar effects, but that non-BZDs may be safer.
  - The authors noted substantial heterogeneity of data which was reduced in subgroup analyses by type of drug. Overall, BZDs and non-BZDs were not significantly different with respect to efficacy.
- A meta-analysis of 22 randomized, DB, PC trials evaluated the safety and efficacy of short-term (14 days) BZDs or zolpidem in the treatment of insomnia in adults < 65 years of age (n = 1894). The treatment duration was ≤ 35 days. It

was found that BZDs and zolpidem produced significant improvements in the primary outcomes (as measured by PSG and self-reporting) of sleep onset latency, number of awakenings, TST, and sleep quality compared to placebo ($p < 0.001$) and their effect sizes were moderate *(Nowell et al 1997).*

- A 2012 meta-analysis that was published using data on the FDA website examined the efficacy and safety of non-BZDs (eszopiclone, zaleplon, zolpidem) using 13 randomized, DB, parallel-group (PG), PC clinical trials (n = 4378). Non-BZDs showed a small, but significant, improvement (reduction) of 22 minutes (95% CI, −33 to −11) in the primary endpoint of PSG sleep latency. For the other primary outcome of subjective sleep latency, non-BZDs showed a small but statistically significant improvement of 7 minutes, compared to placebo. The analyses of effects size showed significant but small to medium differences in PSG sleep latency (WMD -0.36; 95% CI, −0.57 to −0.16) and subjective sleep latency (WMD -0.33; 95% CI, −0.62 to −0.04). The secondary outcomes of TST, PSG and subjective number of awakenings, subjective sleep onset, and sleep quality did not show significant differences, which may have been due to limited data and reporting in the clinical trials *(Huedo-Medina et al 2012).*
- A 2017 meta-analysis of 31 randomized, PG, PC trials with BZDs, non-BZDs (eszopiclone, zaleplon, zolpidem), melatonin agonists, ADPs and other sedating medications was conducted to compare the efficacy of these medications for treatment of primary insomnia. In this meta-analysis, both BZDs and non-BZDs were significantly more effective than ADPs (including low-dose doxepin) in reducing objective sleep onset latency. Also, BZDs were found to be significantly more effective than non-BZDs in reducing subjective sleep onset latency. Non-BZDs demonstrated higher effect sizes for the primary outcomes of objective sleep onset latency and objective TST. Additionally, the pooled effect sizes for all of the outcome variables were statistically significant, indicating small to medium effects *(Winkler and Doering 2014).*
- A meta-analysis that evaluated 234 studies (n = 37,333) was conducted to determine the most efficacious pharmacological treatments for GAD, panic disorder, and SAD. The authors concluded that various studies with SSRIs and SNRIs show that they can be efficacious in the management of anxiety. There was also some evidence for the efficacy of certain BZDs, buspirone, imipramine, hydroxyzine and trifluoperazine. BZDs, however, may cause dependency and are therefore not recommended for routine use *(Baldwin and Polkinghorn 2005).*
- Two 6-month DB, PC, randomized trials (SET and RESET) of tasimelteon in totally blind patients with Non-24 (n = 84) demonstrated that tasimelteon 20 mg given 1 hour before bedtime at the same time every day was well tolerated and entrained the master body clock to a 24-hour clock as measured by urinary 6-sulfatoxymelatonin (aMT6s) and cortisol. During the SET clinical trial, the primary endpoint of sleep entrainment (as measured by aMT6s) was achieved by 20% (8 out of 40) of patients in the tasimelteon group vs. 3% (1 out of 38) of patients in the placebo group (difference of 17%, 95% CI: 3.2 to 31.6, p = 0.0171). A responder analysis demonstrated that 29% of subjects treated with tasimelteon demonstrated clinical response as measured by a ≥ 45-minute improvement in both nighttime and daytime sleep. During the RESET trial, 90% (9 out of 10) of patients in the tasimelteon group vs. 20% (2 out of 10) of patients in the placebo group maintained entrainment (*Lockley et al 2015*).
- A 12-month DB, PG, randomized clinical trial evaluated the safety and efficacy of suvorexant compared to placebo in patients with primary insomnia (n = 781). At Month 1, suvorexant showed greater efficacy than placebo in improving subjective sleep maintenance (TST 22.7 min, 95% CI: 16.4 to 29, p < 0.0001) and subjective time to sleep onset (TSO) (TSO -9.5 min, 95% CI: -14.6 to -4.5, p = 0.0002). These improvements were maintained throughout the 1-year phase (27.5 min in subjective TST, 95% CI: 16.2 to 38.8, p < 0.0001; -9.7 min in subjective TSO, 95% CI: -16.5 to -2.9, p = 0.0055). Over the course of 1 year, the proportion of patients with discontinuation due to AEs or serious AEs was similar among the treatment groups and there was no clinically important difference. The most common AE, somnolence, was reported for 13% of patients who received suvorexant and 3% who received placebo (difference of 10.5%, 95% CI: 6.8 to 14.1) *(Michelson et al 2014).*
- A meta-analysis with 48 studies was conducted to evaluate the efficacy of pharmacological treatments in GAD. The main drug classes compared were the BZDs (diazepam, lorazepam, alprazolam) and the azapirones (buspirone). The BZDs and azapirones were equally effective for anxiety (effect size for BZDs of 0.32, effect size for azapirones of 0.30), although the compliance rate was higher for the BZDs (24.4% drop-out rate vs. 30.7%, respectively, p < 0.05). The author concluded that BZDs and azapirones are effective for the short-term treatment of anxiety, but no drug class is superior in reducing symptoms *(Mitte et al 2005).*

CLINICAL GUIDELINES

Anxiety

- American Academy of Family Physicians (AAFP) Diagnosis and Management of Generalized Anxiety Disorder and Panic Disorder in Adults *(Locke et al 2015)*

- First-line pharmacologic therapies
  - SSRIs
  - SNRIs (duloxetine and venlafaxine ER)
  - buspirone
- Second-line pharmacologic therapies
  - TCAs
  - pregabalin
  - quetiapine
  - hydroxyzine
- Third-line pharmacologic therapies
  - Monoamine oxidase inhibitors (MAOIs)
- The above therapies can be augmented with the addition of BZDs such as alprazolam, clonazepam, diazepam, and lorazepam.

- World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders *(Bandelow et al 2012)*
  - GAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, paroxetine, and sertraline)
        - SNRIs (venlafaxine, duloxetine)
        - pregabalin
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - Imipramine is recommended as second-line therapy
      - BZDs (alprazolam, diazepam) are recommended for patients without a history of dependency
      - Hydroxyzine may be an effective option, although it can cause sedation
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-refractory GAD patients, augmentation of SSRI treatment with atypical antipsychotics (risperidone or olanzapine) may be used.
  - SAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, fluvoxamine, paroxetine, and sertraline)
        - venlafaxine
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - The MAOI phenelzine is effective but less well tolerated than other antidepressants.
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-resistant cases, BZDs (clonazepam) may be used in patients without a history of dependency.
    - Recommendations, grade 4 (evidence from uncontrolled studies)
      - In treatment-resistant cases, the addition of buspirone to an SSRI was effective according to an open study.
- American Psychiatric Association practice guideline for the treatment of patients with panic disorder (second edition) *(Stein et al 2010)*
  - SSRIs, SNRIs, TCAs, and BZDs appear roughly comparable with regard to efficacy for panic disorder; however, SSRIs and SNRIs are recommended as first-line agents due to their relatively favorable safety profile.
  - BZDs may be used adjunctively with antidepressants to treat residual anxiety. BZDs may also be used as monotherapy or in combination with antidepressants for patients who are experiencing distressing symptoms that require rapid symptom control.
  - TCAs should be avoided in patients with acute narrow angle glaucoma or clinically significant prostatic hypertrophy. They may also increase the risk of falls in the elderly.

Insomnia

- American Academy of Sleep Medicine (AASM) Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults *(Sateia et al 2017)*

- Recommendations for the treatment of sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
  - The pharmacologic agents that are recommended:
    - doxepin (low quality of evidence)
    - suvorexant (low quality of evidence)
  - The pharmacologic agents that are not recommended:
    - melatonin (very low quality of evidence)
    - tiagabine (low quality of evidence)
    - trazodone (moderate quality of evidence)
    - tryptophan (high quality of evidence)
    - valerian (low quality of evidence)
- Recommendations for sleep onset and sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
  - The pharmacologic agents that are recommended:
    - eszopiclone (very low quality of evidence)
    - temazepam (moderate quality of evidence)
    - zolpidem (very low quality of evidence)
  - The pharmacologic agent that is not recommended:
    - diphenhydramine (low quality of evidence)
- Recommendations for sleep onset insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
  - The pharmacologic agents that are recommended include:
    - ramelteon (very low quality of evidence)
    - triazolam (high quality of evidence)
    - zaleplon (low quality of evidence)
  - The pharmacologic agents that are not recommended:
    - melatonin (very low quality of evidence)
    - tiagabine (very low quality of evidence)
    - trazodone (moderate quality of evidence)
    - tryptophan (high quality of evidence)
    - valerian (low quality of evidence)

- American College of Physicians (ACP) Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guide *(Qaseem et al 2016)*
  - ACP recommends that all adults receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence).
  - ACP also recommends collaboration with the patient to determine whether a pharmacologic therapy should be initiated (Grade: weak recommendation, low-quality evidence).
    - Low-quality evidence shows that both eszopiclone and zolpidem improved global outcomes in the general population, and low- to moderate-quality evidence shows that eszopiclone, zolpidem, and doxepin improved sleep outcomes, such as sleep onset latency, TST, and WASO.
    - Moderate-quality evidence shows that suvorexant improved treatment response and sleep outcomes in mixed general and adult populations.
    - Low-quality evidence shows no statistically significant difference between ramelteon and placebo for sleep outcomes in the general population.
    - In older adults, low-quality evidence shows that eszopiclone improved global and sleep outcomes and both zolpidem and ramelteon decreased sleep onset latency.
    - Moderate-quality evidence shows that doxepin improved Insomnia Severity Index (ISI) scores, and low- to moderate-quality evidence shows that it improved sleep outcomes.
    - BZDs and melatonin were not included in these guidelines.
    - No one sedative hypnotic was recommended over another, due to insufficient evidence.

SAFETY SUMMARY

Contraindications

- MAOIs are contraindicated for concomitant use with buspirone and doxepin (or within 14 days of discontinuing an MAOI).
- Suvorexant is contraindicated in patients with narcolepsy.
- Quazepam is contraindicated in patients with sleep apnea or chronic pulmonary insufficiency.

Warnings/Precautions

- Boxed warnings
  - BZDs carry a boxed warning for concomitant use with opioids, as it may result in profound sedation, respiratory depression, coma, and death.
- Daytime somnolence, nighttime “sleep-driving,” and depression are listed as warnings for the majority of BZDs and non-BZDs in this review.
- Withdrawal effects can be observed after continuous long-term therapy with BZDs. Abrupt withdrawal or discontinuation should be avoided.
  - Withdrawal effects are mainly anxiety symptoms, but can also include autonomic instability (eg, diaphoresis, increased heart rate), insomnia, and sensory hypersensitivity. The most serious withdrawal effects are seizures and delirium tremens, which can occur with abrupt discontinuation.
- Severe anaphylaxis/anaphylactoid reactions (angioedema) have been reported with eszopiclone, quazepam, ramelteon, temazepam, zalpelon, and zolpidem.
- Worsening of symptoms of depression is considered a warning with most BZDs, eszopiclone, zalpelon, and zolpidem.
- Pregnancy
  - All BZDs are considered highly teratogenic, especially during the first trimester.
  - The non-BZDs have not been studied in pregnant women and are therefore not recommended in this population, unless the potential benefit outweighs the potential risk.
- Elderly
  - BZDs should be used cautiously in the elderly, ie, the lowest possible dose with slow dose up-titration should be utilized. Additionally, BZDs with a short half-life (eg, oxazepam) are preferred over those with a long half-life in the elderly patient population *(Gliatto 2000).*
  - With the non-BZDs, differences in the reported AEs between elderly and younger patients were not noted, however, greater sensitivity of some older patients cannot be ruled out.

AEs

- Drowsiness, sedation, fatigue, cognitive impairment, and muscle weakness are the most frequent AEs with BZD use. Rare AEs include bradycardia, hypotension, rash, urticaria, blurred vision, diplopia, flushing, constipation, nausea, vomiting, change in libido, hepatic dysfunction, and abdominal pain.
- BZD use can lead to physiological dependence and tolerance, especially at higher doses and/or when given for a long duration. Treatment with BZDs should be limited to short-term use whenever possible. All BZDs are Schedule IV controlled substances.
- Somnolence/sedation and other central nervous system (CNS)-related AEs have also been reported with the non-BZD sedative hypnotics.

Drug Interactions

- In general, concomitant use of alcohol and other CNS depressants can increase the risk of CNS depression.
- Most BZDs (except lorazepam, oxazepam, and temazepam) are metabolized to some extent by cytochrome P450 (CYP) 3A4. Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) can increase the risk of toxicity while inducers of CYP3A4 (eg, rifampin) can decrease their effectiveness.
- With the non-BZDs, buspirone, ramelteon (with ketoconazole), suvorexant, zolpidem (with ketoconazole) can increase the risk of toxicity with administered concomitantly with CYP3A4 inhibitors. The efficacy of buspirone, eszopiclone, suvorexant, ramelteon, tasimelteon, zaleplon, and zolpidem may be reduced when these agents are co-administered with CYP3A4 inducers (particularly with rifampin when administered with eszopiclone or ramelteon).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
BZDs				
alprazolam	Tablets	Oral	3 times daily	
chlordiazepoxide	Capsules	Oral	2 to 4 times daily	
clonazepam	Tablets	Oral	Twice daily	
clorazepate	Tablets	Oral	In divided doses or a single dose at bedtime	
diazepam	Tablets, injection	Oral, IV	2 to 4 times daily	
estazolam	Tablets	Oral	At bedtime	
flurazepam	Capsules	Oral	Before retiring	
lorazepam	Tablets, oral concentrate, injection	Oral, IV	2 to 3 times daily for anxiety or a single dose at bedtime for insomnia	
oxazepam	Capsules	Oral	3 to 4 times daily	
temazepam	Capsules	Oral	Before retiring	
triazolam	Tablets	Oral	Before retiring	
quazepam	Tablets	Oral	At bedtime	
Non-BZDs				
buspirone	Tablets	Oral	Twice daily	Not recommended in patients with severe renal or hepatic impairment
doxepin	Tablets	Oral	Within 30 minutes of bedtime	A lower starting dose is recommended in the elderly
eszopiclone	Tablets	Oral	Immediately before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening	
meprobamate	Tablets	Oral	3 to 4 times daily	Not recommended in children < 6 years of age
ramelteon	Tablets	Oral	Within 30 minutes of bedtime	Not recommended in patients with severe hepatic impairment
suvorexant	Tablets	Oral	Within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment
tasimelteon	Capsules	Oral	Before bedtime, at the same time every night	Not recommended in patients with severe hepatic impairment
zaleplon	Capsules	Oral	Immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep	Not recommended in patients with severe hepatic impairment
zolpidem products				
Edluar	Tablets	Sublingual (SL)	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Intermezzo	Tablets	SL	Should be administered when patient wakes in the middle of the night, but has at least 4 hours of bedtime remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Zolpimist	Oral spray	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien	Tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien CR	Extended-release tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men

See the current prescribing information for full details

CONCLUSION

- No specific sedative hypnotic in this review is considered preferable to the others, as each has been shown to have positive effects on sleep latency, TST, and/or WASO in placebo-controlled trials.
- Individual patients may respond differently to these medications and therapy selection, therefore, should be based on consideration of the patient's specific symptom pattern, patient preferences, comorbid disease states, concurrent medications, and the side effect profile for each option *(Schutte-Rodin et al 2008).*
- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent *(Schutte-Rodin et al 2008).*
- Tasimelteon is the only FDA-approved prescription product with proven efficacy for the treatment of Non-24 in totally blind patients.
- Clinical guideline-recommended treatments for GAD include cognitive-behavioral therapy and preferred medications such as SSRIs and SNRIs *(Baldwin et al 2017).*
- Although numerous meta-analyses have been conducted with the anxiolytic and sedative hypnotic classes, they are limited by lack of availability of high quality evidence and considerable variability in design and methodology across clinical trials *(Sateia et al 2017)*.
- All of the BZDs and many of the non-BZD agents are Schedule IV controlled substances due to their propensity to cause physiological dependence. Withdrawal effects can be observed after continuous long-term therapy with many of these agents; therefore, abrupt withdrawal or discontinuation should be avoided.

REFERENCES

- Ambien [package insert], Bridgewater, NJ: Sanofi-Aventis; March 2017.
- Ambien CR [package insert], Bridgewater, NJ: Sanofi-Aventis; December 2016.
- Baldwin D, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. *Int J Neuropsychopharmacol.* 2005;8(2):293-302.
- Baldwin D, Stein MB, Hermann R. Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis. UpToDate Web site. www.uptodate.com. Updated May 26, 2017. Accessed July 20, 2017.
- Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind, D. Efficacy of treatments for anxiety: a meta-analysis. *Int Clin Psychopharmacol.* 2015;30(4):183-192.
- Bandelow B, Sher L, Bunevicius R,et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84.

- Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind, D. Efficacy of treatments for anxiety: a meta-analysis. *Int Clin Psychopharmacol.* 2015;30(4):183-192.
- Barbui C, Cipriani A, Saxena S. Pharmacological treatment of mental disorders in primary health care. WHO Web site. www.WHO.int. Accessed July 20, 2017.
- Belsomra [package insert], Whitehouse Station, NJ: Merck & Co.; May 2016.
- Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007; 22(9):1335-50.
- Buspirone [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc.; December 2016.
- Chlordiazepoxide [package insert], Corona, CA: Watson Laboratories; December 2005.
- Clonazepam [package insert], Corona, CA: Watson Laboratories; March 2008.
- Anxiety disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. http://dsm.psychiatryonline.org. PsychiatryOnline Web site. Accessed July 31, 2017.
- Diazepam [package insert], Parsipanny, NJ: Actavis Pharma; October 2014.
- Doral [package insert], Marietta, GA: Curtis Health; October 2016.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 7, 2017.
- Edluar [package insert], Somerset, NJ: Meda Pharmaceutics, Inc.; October 2014.
- Estazolam [package insert], Parsipanny, NJ: Actavis Pharma, Inc.; November 2014.
- Flurazepam [package insert], Morgantown, WV: Mylan Pharmaceutics, Inc.; June 2013.
- Generalized anxiety disorder among adults. NIH/NIMH Web site. https://www.nimh.nih.gov/health/statistics/prevalence/generalized-anxiety-disorder-among-adults.shtml. Accessed July 26, 2017.
- Gliatto MF. Generalized Anxiety Disorder. *Am Fam Physician*. 2000;62(7):1591-1600.
- Halcion [package insert], New York, NY: Pharmacia and Upjohn Company; December 2016.
- Hetlioz [package insert], Washington, DC: Vanda Pharmaceutics, Inc.; November 2014.
- Huedo-Medina TB, Kirsch I, Middlemass J et al. Effectiveness of non-benzodiazepine hypnotics in the treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ.* 2012;345:e8343.
- Intermezzo [package insert], Stamford, CT: Purdue Pharma; September 2015.
- Locke AB, Kirst N, Shultz C. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician* 2015;91(9):617-624.
- Lockley SW, Dressman MA, Licamele L, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386(10005):1754-64
- Lorazepam [package insert], Huntsville, AL: Qualitest Pharmaceuticals; August 2015.
- Lunesta [package insert], Marlborough, MA: Sunovian Pharmaceutics, Inc.; May 2014.
- Meprobamate [package insert], Eatontown, NJ: Heritage Pharmaceuticals, Inc,; July 2016.
- Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2014;13:461-471.
- Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol.* 2005;25(2):141-150.
- Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF 3rd, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA*. 1997; 278(24):2170-7.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 7, 2017.
- Oxazepam [package insert], Princeton, NJ: Sandoz, Inc.; June 2017.
- Restoril [package insert], St. Louis, MO: Mallinckrodt Pharmaceutics, Inc.; September 2016.
- Rozerem [package insert], Deerfield, IL: Takeda Pharmaceutics, Inc.; November 2010.
- Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guidelines for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(2):307-349.
- Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
- Silenor [package insert], Morristown, NJ: Pernix Therapeutics; March 2010.
- Sonata [package insert], New York, NY: Pfizer, Inc.; May 2013.
- Stein MB, Goin MK, Pollack MH et al. American Psychiatric Association practice guideline for the treatment of patients with panic disorder. 2010. Psychiatry Online Web site. www.psychiatryonline.com. Accessed on July 26, 2017.
- Qaseem A, Kangsara D, Forceia MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165:125-133.
- Tranxene-T [package insert], Lebanon, NJ: Recordati Rare Disease, Inc.; September 2016.
- Winkler A, Doering B K. Drug treatment of primary insomnia: A meta-analysis of polysomnographic randomized controlled trials. *CNS Drugs*. 2014:28:799–816.
- Xanax [package insert], New York, NY: Pharmacia and Upjohn Company; April 2017.
- Zolpimist [package insert], Louisville, KY: Magna Pharmaceutics, Inc.; January 2016.

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Therapeutic Class Overview
Intranasal Antihistamines

INTRODUCTION

- Allergic rhinitis is a condition characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage. Symptoms may also include pruritus of the eyes, palate, and ears (Snellman et al, 2013).
- Allergic rhinitis is common, affecting 10% to 30% of children and adults in the United States (U.S.) and other industrialized countries (Brozek et al, 2010; Wallace et al, 2008). Allergic rhinitis is also referred to in terms of the cyclical or persistent nature of symptoms. Seasonal allergic rhinitis (SAR) is that which occurs at a particular time of the year, whereas perennial allergic rhinitis (PAR) symptoms are present year round.
- Known risks factors for developing allergic rhinitis include family history of atopy, male sex, birth during the pollen season, firstborn status, early use of antibiotics, maternal smoking exposure in the first year of life, exposure to indoor allergens (e.g., dust mite allergen), serum immunoglobulin E (IgE) level >100 IU/mL before 6 years of age, and presence of allergen-specific IgE (Wallace et al, 2008).
- Allergic rhinitis may be classified by its intermittent or persistent pattern and by severity (mild or moderate-severe). Intermittent patterns involve the presence of symptoms for less than 4 days per week or for less than 4 weeks; whereas persistent patterns entail the presence of symptoms more than 4 days per week and for more than 4 weeks (Brozek et al, 2010).
- Mild disease is classified as the presence of symptoms without the presence of sleep disturbances; impairment in school or work performance; impairment in daily activities, leisure and/or sport activities; or troublesome symptoms. If one or more of these complications are present, the condition is considered moderate-severe in nature (Brozek et al, 2010).
- Treatment goals involve resolving symptoms, minimizing morbidity, preventing disease progression, improving the individual's quality of life, minimizing adverse drug events, reducing direct and indirect economic costs associated with disease progression and loss of productivity (e.g., missed work or school days), and ensuring the appropriate step-wise approach of drug therapy to utilize targeted therapies specific to symptomatology and reduce unnecessary healthcare spending (Brozek et al, 2010).
- Non-pharmacologic approaches to preventing and managing the symptoms of allergic rhinitis include allergen avoidance (dust mites, animal dander, mold, and smoke exposure, etc.), nasal saline irrigation, exclusive breastfeeding for at least the first 3 months for all infants irrespective of the family history of atopy, as well as multifaceted interventions to reduce early life exposure to house dust mites (e.g., bed encasings, hard wood flooring vs carpeting, washing bedding in temperatures exceeding 55°C [131°F]) (Brozek et al, 2010; Wallace et al, 2008).
- Pharmacological approaches to managing allergic rhinitis include single-entity and combination agents from the following classes of medications: intranasal antihistamines, intranasal corticosteroids, intranasal cromolyn, intranasal ipratropium, oral non-sedating antihistamines, decongestants, leukotriene receptor antagonists, oral glucocorticoids, immunotherapy, and ocular administration of medications for ocular symptoms, when present (Brozek et al, 2010; Snellman et al, 2013; Wallace et al, 2008).
- This review will focus on the intranasal antihistamines, which include azelastine, olopatadine, and the combination of an intranasal antihistamine with a corticosteroid, azelastine/fluticasone propionate. Azelastine and olopatadine are H_1-receptor antagonists, which block the activity of histamine to relieve the symptoms of allergic rhinitis (Prescribing information: ASTELIN®, 2014; ASTEPRO®, 2015).
- DYMISTA® is a product combining the antihistaminergic activity of azelastine with the effects of the glucocorticoid, fluticasone propionate. The mechanism of action of glucocorticoids is multifactorial in the management of allergic rhinitis. Although the precise mechanism of fluticasone propionate is unknown, this class of agents has been shown to have varying effects on multiple types of cells, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes; as well as other inflammatory mediators such as histamine, eicosanoids, leukotrienes, and cytokines (DYMISTA prescribing information, 2015). Another combination product, TICALAST® (azelastine/fluticasone propionate) nasal kit, is no longer marketed per the manufacturer, Shoreline Pharmaceuticals, Inc.
- Medispan Classes: Nasal Antiallergy and Nasal Agent Combination

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ASTELIN* (azelastine hydrochloride) nasal solution, 137 µg	Mylan Pharmaceuticals, Inc.	11/01/1996	√
ASTEPRO* (azelastine hydrochloride) nasal solution, 0.15% (205.5 µg)	Mylan Pharmaceuticals, Inc.	08/31/2009	√
DYMISTA (azelastine hydrochloride/ fluticasone propionate) nasal suspension, 137 µg/50 µg	Mylan Pharmaceuticals, Inc.	05/01/2012	√†
PATANASE® (olopatadine hydrochloride) nasal solution, 0.6%	Alcon Laboratories, Inc.	04/15/2008	√

*In August 2016, Mylan Pharmaceuticals completed the acquisition of Meda Pharmaceutical products, including branded ASTELIN, ASTEPRO, and DYMISTA. After the acquisition, certain products were no longer marketed including the branded agent ASTELIN and the ASTEPRO 0.1% nasal solution; although, these products are available generically.
†Generic product manufactured by Apotex Inc. was FDA-approved on April 28, 2017 but is not yet on the market.

(DRUGS@FDA, 2017; Mylan Pharmaceuticals press release, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ASTELIN	ASTEPRO	DYMISTA	PATANASE
Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults and children 5 years and older	√	-	-	-
Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in adults and children 12 years and older	√	-	-	-
Relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 years of age and older	-	√	-	-
Relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief	-	-	√	-
Relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older	-	-	-	√
Relief of the symptoms of seasonal allergic rhinitis in adults and children 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older	-	√	-	-

(Prescribing information: ASTELIN, 2014; ASTEPRO, 2015; DYMISTA, 2015; PATANASE, 2015)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Intranasal azelastine has been shown to be safe and effective over 14 days of treatment in placebo-controlled trials (Howland et al, 2011; Lumry et al, 2007; van Bavel et al, 2009).
- When ASTELIN 0.1% and ASTEPRO 0.15% were compared to placebo in a 2-week trial, there was a significantly greater improvement in total nasal symptom score (TNSS) for both ASTEPRO and ASTELIN vs. placebo (P<0.001). In a retrospective analysis, there was a statistical difference in favor of ASTEPRO 0.15% compared to ASTELIN 0.1% (P=0.047) (Shah et al, 2009[a]).
- A meta-analysis compared azelastine hydrochloride nasal spray to other agents used in the management of SAR and PAR which included beclomethasone nasal spray and loratadine combination, terfenadine (not available in the U.S.), oral cetirizine, budesonide nasal spray, ebastine (not available in the U.S.), levocabastine (not available in the U.S) and oral loratadine. The analysis did not identify a statistically significant difference in treatment response, despite multiple analyses. For TNSS, azelastine was more efficacious compared to placebo (effect size, 0.36; 95% confidence interval [CI], 0.26 to 0.46) (Lee et al, 2007).
- The combination of azelastine hydrochloride with fluticasone propionate nasal spray was significantly more effective compared to the individual agents in various symptom scores in a 2-week, multicenter, double-blind, randomized trial. The improvement in TNSS score from baseline was 37.9% for combination therapy compared to 27.1% and 24.8%, respectively, with single-entity fluticasone and azelastine (P<0.05 for the combination vs either agent alone) (Ratner et al, 2008).
- Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores, and quality of life ratings compared to each agent administered as monotherapy (Carr et al, 2012; Hampel et al, 2010; Meltzer et al, 2012).
- In addition, a randomized, active-controlled, open-label study demonstrated that long-term treatment with combination azelastine hydrochloride and fluticasone propionate nasal spray was well-tolerated (Berger et al, 2014).
- A meta-analysis evaluated combination azelastine hydrochloride and fluticasone propionate nasal spray, sublingual allergen immunotherapy (SLIT), second generation H1-antihistamines, nasal corticosteroids, and montelukast for the treatment of SAR. By indirect comparison, grass pollen SLIT tablets had a greater relative clinical impact compared to azelastine hydrochloride and fluticasone propionate nasal spray, second generation H1-antihistamines, and montelukast, and had a similar relative clinical impact as nasal corticosteroids (Devillier et al, 2014).
- Intranasal olopatadine has been proven safe and effective in placebo-controlled trials across a wide range of doses (Fairchild et al, 2007; Hampel et al, 2006; Meltzer et al, 2005; Meltzer et al, 2011; Patel et al, 2007; Ratner et al, 2005).
- Head-to-head studies have not demonstrated any statistically significant differences in efficacy between olopatadine hydrochloride and azelastine hydrochloride (Lieberman et al, 2011; Meltzer et al, 2008; Shah et al, 2009[b]).
- In a single-dose crossover study comparing ASTELIN with PATANASE, 60.6% of patients favored PATANASE, 30.3% favored ASTELIN, and 9.2% had no preference. Mean patient preference was significantly greater with PATANASE than ASTELIN for overall aftertaste, overall preference, and likelihood of use (Meltzer et al, 2008).
- Both ASTELIN and PATANASE significantly reduced vasomotor rhinitis symptom scores from baseline in a 2-week clinical trial; however, the difference between treatments was not statistically significant (Lieberman et al, 2011).
- In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR. A total of 59 randomized controlled trials were selected to compare agents of 6 classes (oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline) for relative efficacy. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on the evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in

nasal and eye symptom resolution compared to either monotherapy. There is a paucity of information about the use of agents for the treatment of SAR in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).
- Guidelines are summarized in the conclusion section of this document.

SAFETY SUMMARY

- There is a warning of central nervous system impairment requiring caution in performing tasks that require mental alertness associated with azelastine hydrochloride.
- Nasal ulcerations, epistaxis, and nasal septal perforation are potential concerns with the use of DYMISTA and PATANASE.
- Since DYMISTA is a combination product containing fluticasone propionate, safety concerns related to corticosteroids exist, including reduction in growth velocity, hypothalamus-pituitary-adrenal axis effects, immunosuppression, localized infections, glaucoma and/or cataract development, as well as drug interactions with concomitant use of agents known to be strong CYP 450 3A4 inhibitors (e.g., ritonavir, ketoconazole, etc.) due to the potential for increased adverse events.
- The most commonly reported adverse events associated with the intranasal antihistamines include headache, epistaxis, bitter taste, nasal discomfort, congestion, and ulcerations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose	Administration Considerations
ASTELIN (azelastine hydrochloride)	Nasal solution: 137 µg per spray (0.1%)	Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults: One or 2 sprays per nostril twice daily. Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in adults: Two sprays per nostril twice daily.	Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in children 5 to 11 years: One spray per nostril twice daily. Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in children 12 years and older: Two sprays per nostril twice daily.	Before initial use, the system should be primed with 4 sprays or until a fine mist appears. When 3 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.
ASTEPRO (azelastine hydrochloride)	Nasal solution: 205.5 µg per spray (0.15%)	Relief of the symptoms of seasonal allergic rhinitis in adults (0.1%, 0.15%): One or 2 sprays per nostril twice daily; or for 0.15% only, 2 sprays per nostril once daily. Relief of the symptoms of perennial allergic rhinitis in adults (0.1%, 0.15%): Two sprays per nostril twice daily.	Relief of the symptoms of seasonal allergic rhinitis in children 12 years and older (0.1%, 0.15%): One or 2 sprays per nostril twice daily; or 2 sprays per nostril once daily. Relief of the symptoms of perennial allergic rhinitis in children 12 years and older (0.1%, 0.15%): Two sprays per nostril twice daily.	Before initial use, the system should be primed with 6 sprays or until a fine mist appears. When 3 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose	Administration Considerations
			Relief of symptoms of seasonal allergic rhinitis in children 6 to 11 years (0.1%, 0.15%): One spray per nostril twice daily. Relief of symptoms of perennial allergic rhinitis in children 6 to 11 years (0.1%, 0.15%): One spray per nostril twice daily. Relief of symptoms of seasonal allergic rhinitis in children 2 to 5 years (0.1%): One spray per nostril twice daily. Relief of symptoms of perennial allergic rhinitis in children 6 months to 5 years (0.1%): One spray per nostril twice daily.	
DYMISTA (azelastine hydrochloride/ fluticasone propionate)	Nasal suspension: 137 µg/50 µg per spray	Relief of symptoms of seasonal allergic rhinitis in adults who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief: One spray per nostril twice daily.	Relief of symptoms of seasonal allergic rhinitis in children 6 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief: One spray per nostril twice daily.	Before initial use, the system should be primed with 6 sprays or until a fine mist appears. When 14 or more days have elapsed without use, the system should be primed with one spray or until a fine mist appears.
PATANASE (olopatadine hydrochloride)	Nasal solution: 665 µg per spray (0.6%)	Relief of the symptoms of seasonal allergic rhinitis in adults: Two sprays per nostril twice daily.	Relief of the symptoms of seasonal allergic rhinitis in children 12 years and older: Two sprays per nostril twice daily. Relief of the symptoms of seasonal allergic rhinitis in children 6 to 11 years: One spray per nostril twice daily.	Before initial use, the system should be primed with 5 sprays or until a fine mist appears. When 7 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ASTELIN (azelastine hydrochloride)	Start at the lower end of the dosing range.	Safety and effectiveness have not been established in children less than 5 years of age.	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
ASTEPRO (azelastine hydrochloride)	Clinical trials did not include a sufficient number of elderly to determine whether they respond differently than younger patients.	Safety and effectiveness have not been established in children less than 6 months of age.	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
DYMISTA (azelastine hydrochloride/ fluticasone propionate)	Start at the lower end of the dosing range.	Effectiveness has not been established in children less than 6 years of age, and safety has not been established in patients less than 4 years of age.†	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
PATANASE (olopatadine hydrochloride)	No dose adjustment required.	Safety and effectiveness have not been established in children less than 6 years of age. ‡	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

***** Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

† The safety of DYMISTA in children 4 to 5 years of age was similar to children 6 to 11 years of age, but efficacy was not established in 4 to 5 year olds.

CONCLUSION

- Allergic rhinitis is a common condition associated with significant morbidity and economic impact, affecting 10 to 30% of children and adults in the U.S. (Wallace et al, 2008).
- This condition is classified according to the severity of symptoms as well as its intermittent or persistent pattern of symptom occurrence (Brozek et al, 2010).
- Consensus guidelines offer multiple treatment options and do not offer a precise step-therapy approach for treating allergic rhinitis (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- Intranasal antihistamines may be more effective than oral antihistamines for treatment of nasal symptoms, specifically for nasal congestion (Seidman et al, 2015).

- Intranasal antihistamines are effective therapies for managing the symptoms of allergic rhinitis; however, intranasal corticosteroids are generally recognized as the most effective single agents for controlling the broad spectrum of allergic rhinitis symptoms and are considered a first-line therapy in patients with moderate to severe symptoms. Intranasal antihistamines are an effective alternative to intranasal corticosteroids and have a faster onset of action than intranasal corticosteroids (Brozek et al, 2010; Glacy et al, 2013; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- The intranasal antihistamines are all considered equally effective treatment options in the management of allergic and vasomotor rhinitis, with no general preference given to one agent over another (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- The overall safety profile of the single-entity, intranasal antihistamines are comparable and all are generally well tolerated.
- ASTELIN is approved for children as young as 5 years old. ASTEPRO 0.15% and PATANASE are approved for use in children as young as 6 years of age. ASTEPRO 0.1% is approved for use in children as young as 6 months of age depending on the indication. DYMISTA is approved in children as young as 6 years of age.
- DYMISTA (azelastine hydrochloride/fluticasone propionate) is a combination product that utilizes both an intranasal antihistamine and an intranasal corticosteroid to manage the symptoms of allergic rhinitis.

REFERENCES

- ASTELIN® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. October 2014.
- ASTEPRO® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. February 2015.
- Berger WE, Shah S, Lieberman, et al. Long-term randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014; 21:179-85.
- Brozek J, Bousquet J, Baena-Cagnani C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
- Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10. doi: 10.1016/j.jaci.2012.01.077.
- Devillier P, Dreyfus JF, Demoly P, et al. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine. 2014, 12:71. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101870/. Accessed May 16, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm Accessed May 16, 2017.
- DYMISTA® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. February 2015.
- Fairchild C, Meltzer E, Roland P. Comprehensive report of the efficacy, safety, quality of life, and work impact of olopatadine 0.6% and olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2007;28:716-23.
- Glacy J, Putnam K, Godfrey S, et al. Treatments for Seasonal Allergic Rhinitis. Comparative Effectiveness Review No. 120. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC098-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed May 16, 2017.
- Hampel FC, Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCL nasal spray 0.4% and olopatadine HCL nasal spray 0.6% compared to vehicle placebo. Allergy and Asthma Proceedings. 2006;27:202-7.
- Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010 Aug;105(2):168-73. doi: 10.1016/j.anai.2010.06.008.
- Howland WC, Amar NJ, Wheeler W, et al. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011 Jul-Aug;1(4):275-9.
- Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. Pharmacotherapy. 2007;27(6):852-9.
- Lieberman P, Meltzer EO, LaForce CF, et al. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% vs azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc. 2011 Mar-Apr;32(2):151-8.
- Lumry W, Prenner B, Corren J, et al. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol. 2007;99:267-72.
- Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011 May-Jun;32(3):213-20.
- Meltzer EO, Garadi R, LaForce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc. 2008;29:659-68.
- Meltzer EO, Hampel FC, Rater PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Annals of Allergy and Asthma Immunology. 2005;95:600-6.
- Meltzer EO, LaForce C, Ratner P, et al. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial of efficacy and safety. Allergy Asthma Proc. 2012 Jul;33(4):324-32.
- Mylan Pharmaceutical press release. Mylan Completes Acquisition of Meda. Website. August 5, 2016. Available at: http://newsroom.mylan.com/2016-08-05-Mylan-Completes-Acquisition-of-Meda. Accessed May 24, 2017.
- PATANASE® prescribing information. Alcon Laboratories, Inc.; Fort Worth, TX. October 2015.
- Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. Otolaryngology-Head and Neck Surgery. 2007;137:918-24.

- Ratner PH, Hampel F, Van Bravel J, et al. Combination therapy with azelastine hydrochloride nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:74-81.
- Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Annals of Allergy, Asthma, & Immunology. 2005;95(5):474-9.
- Seidman MD, Gurgel RK, Lin ST, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):SI-S43.
- Shah S, Berger W, Lumry W, et al. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009[a];30(6):628-33.
- Shah S, Nayak A, Ratner P, et al. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Ther. 2009[b];31(1):99-107.
- Snellman L, Adams W, Anderson G, et al. Diagnosis and Treatment of Respiratory Illness in Children and Adults (Fourth edition; 2013 January). Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_respiratory_guidelines/respiratory_illness/. Accessed May 16, 2017.
- van Bavel J, Howland W, Amar NJ, et al. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(5):512-18.
- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84.

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Therapeutic Class Overview
Intranasal Corticosteroids

INTRODUCTION

- Intranasal corticosteroids are primarily used to treat perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) and may be useful in the treatment of some forms of nonallergic rhinitis (Wallace et al, 2008).
- Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing and/or nasal itching. These symptoms result from a complex allergen-driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators (Wallace et al, 2008).
- Treatment should consist of patient education, allergen avoidance activities and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms.
- Intranasal corticosteroids down-regulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes (Clinical Pharmacology®, 2017).
- Most intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of PAR and SAR. Mometasone (NASONEX®) carries an additional indication for the prophylaxis of SAR. NASACORT ALLERGY 24HR® (triamcinolone acetate), FLONASE® ALLERGY RELIEF (fluticasone propionate), FLONASE® SENSIMIST ALLERGY RELIEF (fluticasone furoate), and RHINOCORT® ALLERGY (budesonide) are all FDA-approved for over-the-counter use (Drugs@FDA, 2017).
- Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction (Wallace et al, 200flu8). Two currently available intranasal corticosteroids, beclomethasone (BECONASE AQ®) and mometasone (NASONEX®) are also FDA-approved for the management of nasal polyps.
- Beclomethasone (BECONASE AQ) and fluticasone propionate are approved for the management of nonallergic rhinitis (eg, infectious rhinitis, hormonal rhinitis and vasomotor nonallergic rhinitis with eosinophilia syndrome). Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events (Wallace et al, 2008).
- Beclomethasone (QNASL™) and ciclesonide (ZETONNA®) are the only two intranasal corticosteroid products formulated as a “dry” nasal aerosol; all other products within the class are formulated as aqueous suspensions.
- Recently, VERAMYST® (fluticasone furoate) was withdrawn from the market after over-the-counter FLONASE® SENSIMIST™ ALLERGY RELIEF (fluticasone furoate) was launched (GlaxoSmithKline press release, 2017; Snyder-Bulik, 2017).
- Continuous administration of intranasal corticosteroids is more efficacious than as-needed dosing, and the onset of therapeutic effect occurs between three and twelve hours (Wallace et al, 2008).
- As a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.
- Medispan Class: Nasal Steroids

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
BECONASE AQ (beclomethasone dipropionate monohydrate)	GlaxoSmithKline	07/27/1987	-
FLONASE ALLERGY RELIEF† (fluticasone propionate)	GlaxoSmithKline	07/23/2014	✔
FLONASE SENSIMIST ALLERGY RELIEF† (fluticasone furoate)	GlaxoSmithKline	08/02/2016	-
flunisolide*	Various	09/24/1981	✔
fluticasone propionate*	Various	10/19/1994	✔
NASACORT ALLERGY 24HR† (triamcinolone acetonide)	Sanofi	10/11/2013	✔
NASONEX (mometasone furoate monohydrate)	Merck Sharp Dohme	10/01/1997	✔
OMNARIS® (ciclesonide)	Sunovion	11/21/2007	-
QNASL (beclomethasone dipropionate)	Teva Branded Pharm	03/23/2012	-
RHINOCORT ALLERGY† (budesonide)	McNeil Consumer Healthcare	03/23/2015	✔
RHINOCORT AQUA (budesonide)	AstraZeneca	10/01/1999	✔
triamcinolone*	Various	05/20/1996	✔
ZETONNA (ciclesonide)	Sunovion	01/20/2012	-

*Brand prescription FLONASE (fluticasone propionate), NASALIDE (flunisolide), and NASACORT AQ (triamcinolone) are no longer marketed; however, generics for these products are available.
†Over-the-counter product

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017; Drug Facts and Comparisons, 2017)

INDICATIONS

Table 2. Food and Drug Administration-Approved Indications

Indication	Beclomethasone	Budesonide	Budesonide (OTC)	Ciclesonide	Flunisolide	Fluticasone furoate	Fluticasone furoate (OTC)	Fluticasone propionate	Fluticasone propionate (OTC)	Mometasone	Triamcinolone	Triamcinolone (OTC)
Indications for Prescription Products												
Treatment/relief of symptoms of SAR and PAR	✔ (age ≥6)*			✔ (age ≥12)†		✔ (age ≥2)						
Treatment of nasal symptoms of SAR	✔ (age ≥4)‡	✔ (age ≥6)		✔ (age ≥6)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment of nasal symptoms of PAR	✔ (age ≥4)‡	✔ (age ≥6)		✔ (age ≥12)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment/relief of nasal congestion associated with SAR										✔ (age ≥2)		
Prophylaxis of nasal symptoms of SAR										✔ (age ≥12)		
Relief of symptoms of nonallergic (vasomotor) rhinitis	✔ (age ≥6)*											
Management of nasal symptoms of perennial nonallergic rhinitis								✔ (age ≥4)				
Treatment of nasal polyps										✔ (age ≥18)		
Prevention of recurrence of nasal polyps following surgical removal	✔ (age ≥6)*											

OTC Uses												
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose			✔ (age ≥6)									✔ (age ≥2)
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes							✔ (age ≥2)‖		✔ (age ≥4)			

OTC = over-the-counter
*Beconase AQ
†Zetonna
‡Qnasl
§Omnaris
‖Itchy, watery eyes use is for patients ≥12 years of age

(Prescribing information: BECONASE AQ, 2015; FLONASE ALLERGY RELIEF, 2015; FLONASE SENSIMIST, 2017; flunisolide, 2016; fluticasone propionate, 2017; NASACORT ALLERGY 24HR, 2016; NASONEX, 2013; OMNARIS, 2016; QNASL, 2016; RHINOCORT ALLERGY, 2016; RHINOCORT AQUA, 2016; triamcinolone, 2013; ZETONNA, 2014)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Daily administration of intranasal corticosteroids is associated with statistically significant improvements in allergy-related total nasal symptom score (TNSS) and health related quality of life scores. Numerous head-to-head clinical trials comparing the available intranasal corticosteroids have generally demonstrated no significant clinical differences among the available intranasal corticosteroids with regard to efficacy. Some studies have reported differences in sensory perceptions and patient preference with one agent compared to another. Patients administering the agents noted differences in odor, aftertaste, and severity of irritation, though these differences were not associated with differences in efficacy between the agents (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2002; Bachert et al, 2004; Berger et al, 2003; Day et al, 1998; Drouin et al 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; Khanna et al, 2005; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993, Yonezaki et al, 2016).
- Head-to-head trials evaluating the efficacy and safety of beclomethasone, fluticasone propionate and flunisolide demonstrate that these agents are comparable to other agents within the class. However, additional results of these studies reinforce that all of the intranasal corticosteroids should be considered equally efficacious (Aasand et al, 1984; Bachert et al, 2004; Berger et al, 2003; Drouin et al, 1996; Mak et al, 2013; McAllen et al, 1980; Meltzer et al, 2010; Meltzer et al, 2008; Ratner et al, 1992; Sahay et al, 1980; Sipila et al, 1983; Small et al, 1997; Stokes et al, 2004; Van As et al, 1993).
- To date, the newly approved intranasal corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. In a six-week study of patients with PAR, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; P<0.001). Furthermore, beclomethasone was associated with a statistically significant improvement in quality of life score compared to placebo (P=0.001) (Meltzer et al, 2012). A two-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 6 to 11 years of age with SAR also demonstrated improvement in reflective TNSS compared to placebo (-1.9 vs -1.2; P<0.001) (Storms et al, 2013). A 12-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 4 to 11 years of age with perennial allergic rhinitis demonstrated improvement in both reflective and instantaneous TNSS compared to placebo (mean treatment difference -0.53 [P=0.009] and -0.52 [P=0.008], respectively) (Berger et al, 2015).
- The aerosolized ciclesonide formulation has also been shown to significantly improve symptoms of allergic rhinitis compared to placebo. In a study by Ratner et al, ciclesonide administered at a daily dose of 80 µg or 160 µg reduced reflective TNSS by 15.1 and 16%, respectively, compared to 3.7% in the placebo group (P<0.001 for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptom scores and quality of life (P<0.001 for both). Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration (Berger et al, 2012; LaForce et al, 2009; Mohar et al, 2012; Ratner et al, 2010; Ratner et al, 2012).
- A systematic review of 40 studies evaluated the use of topical corticosteroids in the treatment or prevention of recurrence of nasal polyps. Topical corticosteroids were effective compared to placebo in the improvement in overall symptoms, nasal obstruction, and a reduction in the size of polyps. Additionally, topical corticosteroids prevented the regrowth of polyps following surgery. No differences in adverse events between topical corticosteroids and placebo were observed (Kalish et al, 2012).
- The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR. A total of 59 randomized controlled trials met inclusion criteria to compare agents of six classes for relative efficacy. Agents included oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in nasal and eye symptom resolution compared to either monotherapy. No information was available about the use of these agents for the treatment of SAR in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).

- A meta-analysis evaluated nasal corticosteroids, sublingual allergen immunotherapy (SLIT), second generation H1-antihistamines, combination azelastine hydrochloride with fluticasone propionate nasal spray, and montelukast for the treatment of SAR. By indirect comparison, nasal corticosteroids and grass pollen SLIT tablets had a greater relative clinical impact on symptom scores compared to azelastine hydrochloride combined with fluticasone propionate nasal spray, second generation H1-antihistamines, and montelukast (Devillier et al, 2014). In a similar indirect, meta-analysis, SLIT (timothy grass and ragweed) and mometasone furoate improved TNSS to a greater extent than montelukast and desloratadine in the treatment of both SAR and PAR (Durham et al, 2016).
- A meta-analysis compared the effects of intranasal corticosteroids for treatment of chronic rhinosinusitis. A total of 9 randomized controlled trials were included. There was no evidence that one intranasal spray was more effective than another for disease severity or disease-specific quality of life. Epistaxis was more common with higher doses compared to lower doses (Chong et al, 2016).
- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another. Intranasal corticosteroids combined with intranasal antihistamines are considered to be more effective than either alone in the treatment of allergic rhinitis. Addition of oral antihistamines is not effective (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).

SAFETY SUMMARY

- The intranasal corticosteroids are contraindicated in patients with an untreated infection of the nasal mucosa.
- Intranasal corticosteroids should not be used in patients with recent nasal septal ulcers, nasal surgery or trauma, as they may impair wound healing.
- Systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur when intranasal steroids are used at higher-than-recommended doses or in susceptible individuals at recommended doses. Patients using corticosteroids may be more susceptible to infection; specific effects of the dose, route and duration of use are not known.
- However, as a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.

(Drug Facts and Comparisons, 2017)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Adult Dose	Usual Recommended Pediatric Dose	Administration Considerations
Beclomethasone (BECONASE AQ, QNASL)	Aerosol for nasal inhalation (QNASL): 40 µg/actuation (60 actuations) & 80 µg/actuation (120 actuations) Suspension for nasal inhalation (BECONASE AQ): 42 µg/inhalation (180 sprays)	PAR, SAR: Aerosol: 320 µg daily, administered as two actuations (80 µg strength) in each nostril once daily Suspension: one to two sprays in each nostril twice daily Nasal polyps, nonallergic (vasomotor) rhinitis: Suspension: one to two sprays in each nostril twice daily	Nasal polyps, nonallergic (vasomotor) rhinitis, PAR, SAR in children 6 to 12 years old: Suspension: initial, one inhalation in each nostril twice daily; maximum, two inhalations in each nostril twice daily PAR, SAR in children 4 to 11 years of age: Aerosol: 80 µg daily, administered	Suspension: The unit should be primed by releasing six sprays before initial use. If the pump is not used for seven days, it should be re-primed until a fine spray appears. Aerosol: The unit should be primed by releasing four sprays before

Drug	Dosage Form: Strength	Usual Recommended Adult Dose	Usual Recommended Pediatric Dose	Administration Considerations
			as one actuation (40 µg strength) in each nostril once daily	initial use. If not used for seven days, it should be re-primed by releasing two sprays.
Budesonide (RHINOCORT ALLERGY, RHINOCORT AQUA)	Rx suspension (RHINOCORT AQUA): 32 µg/inhalation (120 sprays) OTC suspension (RHINOCORT ALLERGY): 32 µg/inhalation (60 or 120 sprays)	PAR, SAR: Rx suspension: one spray in each nostril once daily; maximum, four sprays in each nostril once daily Hay fever or other upper respiratory allergies: OTC suspension: two sprays in each nostril once daily; once symptoms improve, reduce to one spray in each nostril once daily	PAR, SAR in children 6 to 12 years old: Rx suspension: one spray in each nostril once daily; maximum, two sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 6 to 12 years old: OTC suspension: one spray in each nostril once daily; maximum, two sprays in each nostril once daily	The unit should be primed by releasing eight sprays before initial use. If not used for two consecutive days, it should be re-primed with one spray or until a fine spray appears.
Ciclesonide (OMNARIS, ZETONNA)	Aerosol for nasal inhalation (ZETONNA): 37 µg/actuation (60 actuations) Suspension for nasal inhalation (OMNARIS): 50 µg/inhalation (120 sprays)	PAR, SAR: Aerosol: one inhalation in each nostril once daily Suspension: two sprays in each nostril once daily	SAR in children ≥6 years old: Suspension: two sprays in each nostril once daily	Suspension: The unit should be primed by releasing eight sprays before initial use. If not used for four consecutive days, it should be re-primed with one spray or until a fine mist appears. Aerosol: The unit should be primed by actuating three times before initial use. If not used for ten consecutive days, it must be re-primed by actuating three times.

Drug	Dosage Form: Strength	Usual Recommended Adult Dose	Usual Recommended Pediatric Dose	Administration Considerations
Flunisolide	Suspension for nasal inhalation: 25 µg/inhalation (200 sprays)	PAR, SAR: Suspension: two sprays in each nostril twice daily; maximum, eight sprays in each nostril per day	PAR, SAR in children six to 14 years old: Suspension: one spray in each nostril three times daily or two sprays in each nostril twice daily; maximum, four inhalations in each nostril per day	The unit should be primed before initial use by releasing five or six sprays. It must be re-primed if it has not been used for five days or more, or if it has been disassembled for cleaning.
Fluticasone furoate (FLONASE SENSIMIST)	OTC suspension for nasal inhalation (FLONASE SENSIMIST): 27.5 µg/inhalation (30, 60, or 120 sprays)	Hay fever or other upper respiratory allergies: OTC suspension: two sprays in each nostril once daily for one week; maintenance, one or two sprays in each nostril once daily, as needed to treat symptoms	Hay fever or other upper respiratory allergies in children 2 to 11 years of age: OTC suspension: one spray in each nostril once daily	OTC suspension: The unit should be primed before initial use, when not used for 30 days or longer, or if the cap has been left off for five days or longer, by spraying until a fine mist appears.
Fluticasone propionate (FLONASE ALLERGY RELIEF, fluticasone)	Rx suspension for nasal inhalation: 50 µg/inhalation (120 sprays) OTC suspension for nasal inhalation: 50 µg/inhalation (30, 60 or 120 sprays)	Perennial nonallergic rhinitis: Rx suspension: two sprays in each nostril once daily or one spray in each nostril twice daily; patients may be able to reduce dose to one spray in each nostril once daily for maintenance therapy Hay fever or other upper respiratory allergies: OTC suspension: two sprays in each nostril once daily for one week; maintenance, one or two sprays in each nostril once daily, as needed to treat symptoms	Perennial nonallergic rhinitis in children 4 years of age and older: Rx suspension: one spray in each nostril once daily; maximum, two sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 4 to 11 years of age: OTC suspension: one spray in each nostril once daily	Rx suspension: The unit should be primed by releasing six sprays until a fine spray appears before initial use and if not used for a week or more. OTC suspension: The unit should be primed by spraying until a fine mist appears before initial use, if not used for one week or more, and after cleaning the nozzle.
Mometasone (NASONEX)	Suspension for nasal inhalation:	PAR, SAR: Suspension: two sprays	PAR, SAR in children 2 to 11	The unit should be primed

Drug	Dosage Form: Strength	Usual Recommended Adult Dose	Usual Recommended Pediatric Dose	Administration Considerations
	50 µg/inhalation (120 sprays)	in each nostril once daily Nasal polyps in adults ≥18 years old: Suspension: two sprays in each nostril once or twice daily	years old: Suspension: one spray in each nostril once daily	before initial use by actuating 10 times or until a fine spray appears. If unused for more than seven days, it should be re-primed by actuating two times or until a fine spray appears.
Triamcinolone (triamcinolone, NASACORT ALLERGY 24HR)	Rx suspension for nasal inhalation (triamcinolone): 55 µg/inhalation (120 sprays) OTC suspension for nasal inhalation (NASACORT ALLERGY 24HR): 55 µg/inhalation (30, 60, or 120 sprays)	SAR and PAR: Rx suspension: two sprays in each nostril once daily; maintenance, one spray in each nostril once daily. Hay fever or other upper respiratory allergies: OTC suspension: two sprays in each nostril once daily; maintenance, one inhalation in each nostril once daily	SAR and PAR in children 6 to 12 years old: One spray in each nostril once daily; maximum, two sprays in each nostril once daily SAR and PAR in children 2 to 5 years old: One spray in each nostril once daily Hay fever or other upper respiratory allergies in children 6 to under 12 years: OTC Suspension: one spray in each nostril once daily; maximum, two sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 2 to under 6 years: OTC Suspension: one spray in each nostril once daily	Rx suspension: The unit should be primed before initial use by releasing five sprays. If not used for more than two weeks, it can be re-primed with one spray. OTC suspension: The unit should be primed before initial use and if not used for more than two weeks by spraying until a fine mist is produced.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Beclomethasone	No dosage adjustment required in the elderly population.	BECONASE AQ is approved for use in children 6 years of age and older. QNASL is approved for use in children 4 years of age and older.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category C Unknown whether excreted in breast milk
Budesonide	No dosage adjustment required in the elderly population.	Approved for use in children 6 years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Excreted in breast milk
Ciclesonide	No dosage adjustment required in the elderly population.	OMNARIS is approved for use in children 6 years of age and older for SAR and ages 12 years and older for PAR. ZETONNA is approved for use in children 12 years of age and older.	Not studied in renal dysfunction.	No dosage adjustment required.	Pregnancy Category C Unknown whether excreted in breast milk
Flunisolide	No dosage adjustment required in the elderly population.	Approved for use in children 6 years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk
Fluticasone furoate	No dosage adjustment required in the elderly population.	Approved for use in children 2 years of age and older.	No dosage adjustment required.	No dosage adjustment required. Monitoring is recommended with moderate and severe hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Fluticasone propionate	No dosage adjustment required in the elderly population.	Approved for use in children 4 years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk
Mometasone	No dosage adjustment required in the elderly population.	Approved for use in children 2 years of age and older for treatment of SAR and PAR (age ≥12 years for prophylaxis of SAR and age ≥18 years for nasal polyps).	Not studied in renal dysfunction.	No dosage adjustment required.	Pregnancy Category C Unknown whether excreted in breast milk
Triamcinolone	No dosage adjustment required in the elderly population.	Approved for use in children 2 years of age and older.	No dosage adjustment required.	No dosage adjustment required.	Pregnancy Category C Unknown whether excreted in breast milk

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Intranasal corticosteroids are used for the management of allergic rhinitis, some forms of nonallergic rhinitis and nasal polyps. They are generally well tolerated and are associated with limited drug interactions due to their localized administration and limited systemic absorption. Like other corticosteroids, intranasal corticosteroids carry warnings regarding use in patients with active infection and the development of signs of adrenal insufficiency, particularly with the administration of higher-than-recommended doses (Wallace et al, 2008).
- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- All available intranasal corticosteroids have demonstrated safety and efficacy for their respective indications. These agents have been shown to be effective in reducing rhinitis-related nasal symptoms such as congestion, rhinorrhea, sneezing, nasal itch, and postnasal drip. The differences in tolerability and sensory perceptions noted in clinical trials were minor and did not translate into differences in outcomes. The results of multiple head-to-head trials have generally failed to demonstrate clinically significant differences between products (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2004; Bachert et al; 2002; Berger et al, 2003; Day et al, 1998; Drouin et al. 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993).
- Two nasal aerosol formulations, beclomethasone (QNASL) and ciclesonide (ZETONNA), have been approved by the FDA for the relief of symptoms associated with PAR and SAR. The other intranasal corticosteroid products are

formulated as aqueous suspensions, which may be bothersome to patients due to the potential of the suspension to drip down or out of the nose following administration.

REFERENCES

- Aasand G, Etholm BO, Skjostad M, Volden J. Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis. Rhinology. 1982;20(4):205-11.
- Al-Mohaimeid H. A parallel-group comparison of budesonide and beclomethasone dipropionate for the treatment of perennial allergic rhinitis in adults. J Int Med Res. 1993;21(2):67-73.
- Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology. 1995;33(1):18-21.
- Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89:292-7.
- Bachert C, Lukat KF, Lange B. Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity in healthy volunteers. Clin Exp Allergy. 2004;34:85-90.
- BECONASE AQ prescribing information. GlaxoSmithKline. Research Triangle Park, NC. September 2015.
- Berger WE, Jacobs RL, Amar NJ, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in children with perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2015 Aug;115(2):130-6.
- Berger WE, Kaiser H, Gawchik SM, et al. Triamcinolone acetonide aqueous nasal spray and fluticasone propionate are equally effective for relief of nasal symptoms in patients with seasonal allergic rhinitis. Otolaryngol Head Neck Surg. 2003 Jul;129(1):16-23.
- Berger WE, Mohar DE, LaForce C, et al. A 26-week tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Am J Rhinol Allergy. 2012 Jul;26(4):302-7.
- Brozek J, Bousquet J, Baena-Cagnani C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
- Chong LY, Head K, Hopkins C, et al. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016 Apr 26;4:CD011993. doi: 10.1002/14651858.CD011993.pub2.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc; 2017. Available at: http://www.clinicalpharmacology.com. Accessed May 22, 2017.
- Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 1998;102(6):902-8.
- Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine. 2014, 12:71. DOI: 10.1186/1741-7015-12-71.
- Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol. 1996:77(2):153-60.
- Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2017. Available at: https://fco.factsandcomparisons.com. Accessed May 22, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 22, 2017.
- Durham SR, Creticos PS, Nelson HS, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: pooled analyses. J Allergy Clin Immunol. 2016;138(4):1081-1088.
- FLONASE ALLERGY RELIEF drug facts. GlaxoSmithKline. November 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205434s003lbl.pdf. Accessed May 22, 2017.
- FLONASE SENSIMIST ALLERGY RELIEF drug facts. GlaxoSmithKline. April 2017. Available at: https://www.accessdata.fda.gov. Accessed May 22, 2017.
- Flunisolide prescribing information. Bausch & Lomb Inc. Tampa, FL. June 2016.
- Fluticasone propionate prescribing information. West-Ward Pharmaceuticals Corp. Eatontown, NJ. April 2017.
- Glacy J, Putnam K, Godfrey S, et al. Treatments for seasonal allergic rhinitis. Comparative Effectiveness Review No. 120. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC098-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2013.
- GlaxoSmithKline (GSK) press release. GSK Consumer Healthcare Launches Flonase Sensimist Allergy Relief Nationwide. Website. February 8, 2017. Available at: http://us.gsk.com/en-us/media/press-releases/2017/gsk-consumer-healthcare-launches-flonase-sensimist-allergy-relief-nationwide/. Accessed May 24, 2017.
- Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. Journal of Allergy and Clinical Immunology. 1996:98(4):724-31.
- Gross G, Jacobs RL, Woodworth TH, et al. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2002;89(1):56-62.
- Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology. 1993;31(4):169-74.
- Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex™) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy. 1996;51:569-76.
- Kalish L, Snidvongs K, Sivasubramaniam R, et al. Topical steroids for nasal polyps. Cochrane Database of Systematic Reviews. 2012, Issue 12. Art. No.: CD006549. DOI: 10.1002/14651858.CD006549.pub2.
- Khanna P, Shah A. Assessment of sensory perceptions and patient preference for intranasal corticosteroid sprays in allergic rhinitis. Am J Rhinol. 2005;19(3):316-21.
- LaForce C, van Bavel J, Meltzer EO, et al. Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2009 Aug;103(2):166-73.
- LaForce CF, Dockhorn RJ, Findlay SR, et al. Fluticasone propionate: an effective alternative treatment for seasonal allergic rhinitis in adults and adolescents. J Fam Pract. 1994;38:145-52.

- Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. Curr Med Res Opin. 1984;9:290-5.
- Lumry W, Hampel F, LaForce C, et al. A comparison of once-daily triamcinolone acetonide aqueous and twice-daily beclomethasone dipropionate aqueous nasal sprays in the treatment of seasonal allergic rhinitis. Allergy Asthma Proc. 2003;24:203-10.
- Mak KK, Ku MS, Lu KH, et al. Comparison of mometasone furoate monohydrate (Nasonex) and fluticasone propionate (Flixonase) nasal sprays in the treatment of dust mite-sensitive children with perennial allergic rhinitis. Pediatr Neonatol. 2013 Aug; 54:239-245. DOI: 10.1016/j.pedneo.2013.01.007.
- Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. The 194-079 Study Group. Ann Allergy Asthma Immunol. 1997:79(3):237-45.
- McAllen MK, Portillo PR, Parr EJ, et al. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest. 1980;74:32-6.
- McArthur JG. A comparison of budesonide and beclomethasone dipropionate sprays in the treatment of seasonal allergic rhinitis. Clin Otolaryngol Allied Sci. 1994;19(6):537-42.
- Meltzer E, Andrews C, Journeay G, et al. Comparison of patient preference for sensory attributes of fluticasone furoate or fluticasone propionate in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double blind study. Ann Allergy Asthma Immunol. 2010;104:331-8.
- Meltzer E, Stahlman J, Leflein J, et al. Preferences of adult patients with allergic rhinitis for the sensory attributes of fluticasone furoate vs fluticasone propionate nasal sprays: a randomized, multicenter, double-blind, single-dose, crossover study. Clin Ther. 2008;30:271-9.
- Meltzer EO, Bardelas J, Goldsobel A, Kaiser H. A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis. Treat Respir Med. 2005;4(4):289-96.
- Meltzer EO, Jacobs RL, LaForce CF, et al. Safety and efficacy of once-daily treatment with beclomethasone dipropionate nasal aerosol in subjects with perennial allergic rhinitis. Allergy Asthma Proc. 2012 May-Jun;33(3):249-57.
- Mohar D, Berger WE, LaForce C, et al. Efficacy and tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Allergy Asthma Proc. 2012 Jan-Feb;33(1):19-26.
- Naclerio RM, Baroody FM, Bidani N, et al. A comparison of nasal clearance after treatment of perennial allergic rhinitis with budesonide and mometasone. Otolaryngol Head Neck Surg. 2003;128:220-7.
- NASACORT ALLERGY 24HR drug facts. Chattem. August 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020468Orig1s042lbl.pdf. Accessed May 22, 2017.
- NASONEX prescribing information. Schering Corporation. Whitehouse Station, NJ. March 2013.
- OMNARIS prescribing information. Sunovion Pharmaceuticals. Marlborough, MA. March 2016.
- QNASL prescribing information. Teva Respiratory. Horsham, PA. February 2016.
- Ratner P, Jacobs R, Mohar D, et al. Evaluation of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol, 80 or 160 µg once daily, for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2010 Dec;105(6):471-9. DOI: 10.1016/j.anai.2010.09.024.
- Ratner PH, Andrews C, Martin B, et al. A study of the efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol in patients with seasonal allergic rhinitis from mountain cedar pollen. Allergy Asthma Proc. 2012 Jan-Feb;33(1):27-35.
- Ratner PH, Paull BR, Findlay SR, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. J Allergy Clin Immunol. 1992;90:285-91.
- RHINOCORT ALLERGY drug facts. AstraZeneca. August 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020746Orig1s036lbl.pdf. Accessed May 22, 2017.
- RHINOCORT AQUA prescribing information. AstraZeneca. Wilmington, DE. January 2017.
- Sahay JN, Chatterjee SS, Engler C. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy. 1980;10:65-70.
- Seidman MD, Gurgel RK, Lin ST, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):SI-S43.
- Shah SR, Miller C, Pethick N, et al. Two multicenter, randomized, single-blind, single-dose, crossover studies of specific sensory attributes of budesonide aqueous nasal spray and fluticasone propionate nasal spray. Clin Ther. 2003;25(8):2198-214.
- Sipila P, Sorri M, Ojala K, Palva A. Comparative trial of flunisolide and beclomethasone dipropionate nasal sprays in patients with seasonal allergic rhinitis. Allergy. 1983;38:303-7.
- Small P, Houle PA, Day JH, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. J Allergy Clin Immunol. 1997;100(5):592-5.
- Snellman L, Adams W, Anderson G, et al. Diagnosis and treatment of respiratory illness in children and adults (Fourth edition; 2013 January). Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/guidelines. Accessed May 22, 2017.
- Snyder-Bulik B. GSK looks for another OTC allergy crossover hit in newly launched Flonase Sensimist. Website. FiercePharma. Feburary 14, 2017. Available at: http://www.fiercepharma.com/marketing/gsk-launches-another-otc-allergy-crossover-flonase-sensimist-and-supporting-ad-campaign. Accessed May 24, 2017.
- Stern MA, Dahl R, Nielsen LP, et al. A comparison of aqueous suspensions of budesonide nasal spray (128 µg and 256 µg once daily) and fluticasone propionate nasal spray (200 µg once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol. 1997;11(4):323-30.
- Stokes M, Amorosi SL, Thompson D, et al. Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal sprays in patients with allergic rhinitis. Otolaryngol Head Neck Surg. 2004;131:225-31.
- Storms WW, Segall N, Mansfield LE, et al. Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2013;111(5):408-414.e1.
- Svendsen UG, Frolund L, Madsen F, et al. Beclomethasone dipropionate vs flunisolide as topical steroid treatment in patients with perennial rhinitis. Clin Otolaryngol Allied Sci. 1989;14(5):441-5.
- Triamcinolone acetonide prescribing information. Winthrop U.S. Bridgewater, NJ. July 2013.
- Van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. J Allergy Clin Immunol. 1993;91(6):1146-54.
- Vanzieleghem MA, Juniper EF. A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immunol. 1987;79(6):887-92.
- Varshney J, Varshney H, Dutta SK, Hazra A. Comparison of sensory attributes and immediate efficacy of intranasal ciclesonide and fluticasone propionate in allergic rhinitis: a randomized controlled trial. Indian J Pharmacol. 2012 Sep-Oct;44(5):550-4. DOI: 10.4103/0253-7613.

- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84. Available at: http://www.allergyparameters.org/published-practice-parameters/alphabetical-listing/rhinitis-download/. Accessed May 22, 2017.
- Welsh PW, Stricker WE, Chu C, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc. 1987;62:125-34.
- Winder J, Bell T, Brodsky L. A comparative study of intranasal triamcinolone acetonide aerosol and intranasal beclomethasone dipropionate aqueous spray in perennial allergic rhinitis. Immunol Allergy Pract. 1993;15(7):203-9.
- Yonezaki M, Akiyama K, Karaki M, et al. Preference evaluation and perceived sensory comparison of fluticasone furoate and mometasone furoate intranasal sprays in allergic rhinitis. Auris Nasus Larynx. 2016;43(3):292-7.
- ZETONNA prescribing information. Sunovion Pharmaceuticals. Marlborough, MA. October 2014.

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