Nevada Medicaid Drug Use Review Board Meeting

April 30, 2020

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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	March 26, 2020
Date of Meeting:	April 30, 2020 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).
Place of Meeting:	Please use the teleconference/WebEx options provided below. If accommodations are requested, please advise using the information at the end of this agenda. Out of deference to Declaration of Emergency Directive 006 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/Declaration-of-Emergency-Directive-006-re-OML.3-21-20.pdf) from the State of Nevada Executive Department signed by Governor Sisolak as well as Emergency Directive 003 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/2020-03-20.Declaration-of-Emergency-Directive-003.pdf) signed March 20, 2020, a physical location will not be open to the public for attendance at this time.

Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email tbenitez@dhcfp.nv.gov or call (775) 684-3730 and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.*

Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e0a7030f0e87a1bc1f03d3eb085e0a6ec Or go to www.webex.com and enter the Event Number listed below. Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.
Event Number:	641 557 826 Click "Join Now"

Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet.

A password should not be necessary, but if asked use: Medicaid1!

For Audio Only:

Phone: 1-763-957-6300
Event: 641 557 826

[Please place your phone on mute unless providing public comment.]

AGENDA

1. Call to Order and Roll Call

2. Public Comment on Any Matter on the Agenda (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to tbenitez@dhcfp.nv.gov. There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. This guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations.*)

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from January 23, 2020.

b. Status Update by the DHCFP.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for calcitonin gene-related peptide (CGRP) receptor inhibitors.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for cystic fibrosis agents.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.

3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for narcolepsy agents.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for sickle cell anemia agents.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for proton pump inhibitors.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for tobacco cessation products.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Toradol® (ketorolac tromethamine) tablets.

1. Public comment on proposed clinical prior authorization criteria.
2. Presentation of utilization and clinical information.
3. Discussion by Board and review of utilization data.
4. Proposed adoption of updated prior authorization criteria.

5. Public Comment on any DUR Board Requested Report

6. DUR Board Requested Reports

a. Opioid utilization – top prescribers and members.

1. Discussion by the Board and review of utilization data.

2. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

b. Methadone utilization and place of service.

1. Discussion by the Board and review of utilization data.
2. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

c. Antibiotic utilization.

1. Discussion by the Board and review of utilization data.
2. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

7. Public Comment on any Standard DUR Report

8. Standard DUR Reports

a. Review of Prescribing/Program Trends.

1. Top 10 Therapeutic Classes for Q3 2019 and Q4 2019 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

1. Review of Q4 2019.
2. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

1. Status of previous quarter.
2. Status of current quarter.
3. Review and discussion of responses.

9. Closing Discussion

a. Public comments on any subject. (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to tbenitez@dhcfp.nv.gov. There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).*)

b. Date and location of the next meeting.

1. Discussion of the time 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 three minutes and written comments are encouraged if possible.**

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov as well as Carson City, Las Vegas, and Reno central offices for the Division of Health Care Financing and Policy. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). At this time, in deference to Emergency Directive 006 dated March 22, 2020 and related directives which have discouraged certain in-person activities, notice has not been posted at other physical locations.

If you require a physical copy of supporting material for the public meeting, please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). Supporting material will also be posted online as referenced above.

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

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated 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 tbenitez@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 3: The requirements contained in NRS 241.020 (4) (a) that public notice agendas be posted at physical locations within the State of Nevada are suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 4: Public bodies must still comply with requirements in NRS 241.020 (4)(b) and NRS 241.020 (4)(c) that public notice agendas be posted to Nevada's notice website and the public body's website, if it maintains one along with providing a copy to any person who has requested one via U.S. mail or electronic mail.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 5: The requirement contained in NRS 241.020 (3)(c) that physical locations be available for the public to receive supporting material for public meetings is suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for

the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

Summary of the DUR Board

Drug Use Review Board

The Drug Use Review Board (DUR) is a requirement of the Social Security Act, Section 1927 and operates in accordance with Nevada Medicaid Services Manual, Chapter 1200 – Prescribed Drugs and Nevada Medicaid Operations Manual Chapter 200.

The DUR Board consists of no less than five members and no more than ten members appointed by the State Director of Health and Human Resources. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist.

The DUR Board meets quarterly to monitor drugs for:

- therapeutic appropriateness,
- over or under-utilization,
- therapeutic duplications,
- drug-disease contraindications
- quality care

The DUR Board does this by establishing prior authorization and quantity limits to certain drugs/drug classes based on utilization data, experience, and testimony presented at the DUR Board meetings. This includes retrospective evaluation of interventions, and prospective drug review that is done electronically for each prescription filled at the Point of Sale (POS).

Meetings are held quarterly and are open to the public. Anyone wishing to address the DUR Board may do so. Public comment is limited to five minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each board member and a copy (electronic preferred) for the official record.

The mission of the Nevada DUR Board is to work with the agency to improve medication utilization in patients covered by Medicaid. The primary goal of drug utilization review is to enhance and improve the quality of pharmaceutical care and patient outcomes by encouraging optimal drug use.

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair

Netochi Adeolokun, Pharm.D., Vice Chair

Mark Canty, MD

Jessica Cate, Pharm.D.

Dave England, Pharm D

Mohammad Khan, MD

Brian Le, DO

James Marx, MD

Michael Owens, MD

Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2020

Date	Time	Location
April 30, 2020	1:00 PM	Hyatt Place, Reno, NV
July 23, 2020	1:00 PM	Hyatt Place, Reno, NV
October 29, 2020	1:00 PM	Hyatt Place, Reno, NV

Web References

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Drug Use Review Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/DUR_Bylaws_draft.pdf

Drug Use Review Board Meeting Material:

https://www.medicaid.nv.gov/providers/rx/dur/DURBoard.aspx

Social Security Act, 1927:

https://www.ssa.gov/OP_Home/ssact/title19/1927.htm

Meeting Minutes

DRUG USE REVIEW BOARD

Date of Meeting: Thursday, January 23, 2020 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), Drug Use Review Board (DUR)

Place of Meeting: Hyatt Place Reno – Tahoe Airport
1790 E Plumb Ln
Reno, NV 89502
Phone: (775) 826-2500

ATTENDEES

Board Members Present
Jennifer Wheeler, Pharm.D., Chair
Netochi Adeolodun, Pharm.D.
Mark Canty, MD
Dave England, Pharm.D.
Mohammad Khan, MD
Jim Tran, Pharm.D.
Michael Owens, MD
Brian Le, DO
Jessica Cate, Pharm.D.

Board Members Absent
None

DHCFP
Holly Long, Social Services Program Specialist
Beth Slamowitz, Pharm.D.
Homa Woodrum, Deputy Attorney General
Tammy Moffitt, Social Services Chief III, Pharmacy Services
Antonio Gudino, Social Services Program Specialist
DuAne Young, Deputy Administrator

DXC
Jovanna Leid, Pharm.D.

OptumRx
Carl Jeffery, Pharm.D.

Managed Care Organizations (MCO)
Thomas Beranek – Silver Summit Health Plan
Ryan Bitton – Health Plan of Nevada
Lisa Todd – Anthem

Public
Scott Burns, J&J
Amy Rodenburg, Allergan
Melissa Sommers, Novartis
Sandy Sierawski, Pfizer
Michael Zarob, Alkermes
Jeana Colabianchi, Sunovion
Georgette Dzwilewski, Indivior
Kaysen Bala, Biogen
Brian McKenna, Tricida
Patrick Moty, Horizon Therapeutics
Kelvin Yamashito, Genzyme
Anne VanBeveren, Scilex
Gary Philips, Jazz Pharm
Joe Ferroli, Takeda
Kevin Aholt, Neurelis
Nicole Robling, Otsuka
Hiten Pateda, Otsuka
Allison Genco, Ferrari Public Affairs

Public Online:
Daniel C Medina
Ashley Cruz, Carrara Nevada
Dawn Dynak, Gilead
Jenna Gianninoto, Abbvie

AGENDA

1. Call to Order and Roll Call

Jennifer Wheeler, Chair: Calls the meeting to order 1:02 PM. We will start with a roll call.

Jennifer Wheeler, Chair: Pharmacist

Homa Woodrum: Homa Woodrum, Deputy Attorney General

Jovanna Leid: Jovanna Leid, DXC

Carl Jeffery: Carl Jeffery, OptumRx

Holly Long: Holly Long, DHCFP

Antonio Gudino-Vargas: Antonio Gudino-Vargas, DHCFP

Beth Slamowitz: Beth Slamowitz, DHCFP

Tammy Moffitt: Tammy Moffitt, DHCFP

Duane Young: Duane Young, DHCFP

Lisa Todd: Lisa Todd, Anthem

Tom Beranek: Tom Beranek, SilverSummit

Ryan Bitton: Ryan Bitton, Health Plan of Nevada

Dave England: Dave England, Pharmacist

Jessica Cate: Jessica Cate, Pharmacist

Jim Tran: Jim Tran, Pharmacist

Brian Le: Brian Le, Physician

Michael Owens: Michael Owens, Physician

Netochi Adeolokun: Netochi Adeolokun, Pharmacist

Mark Canty: Mark Canty, Physician

Public Comment on Any Matter on the Agenda

Jennifer Wheeler, Chair: Do we have any public comments on any agenda item?

Administrative

Jennifer Wheeler, Chair: I'd like to call for action to approve the minutes from the October 17, 2019 meeting.

Motion and second. Voting, ayes across the board, the motion carries.

Holly Long: My name is Holly Long with the DHCFP and I will be providing the update today. The DHCFP made revisions to MSM Chapter 1200 Appendix A based on the recommendations approved at the July 25, 2019 DUR Board meeting. Those recommended changes included revisions to the prior authorization criteria for growth hormones and anti-migraine medications and the criteria for Spravato and gastrointestinal agents. I wanted everyone to know these were effective on December 2, 2019. Recently HHS published an updated guide for clinicians on appropriate dosage reduction and discontinuation of opioid analgesics. A link to the publication has been posted an can be found at the DHCFP pharmacy services site under the education tab. Effective January 6, 2020, Nevada Medicaid fee-for-service transitioned coverage of insulin systems and supplies and continuous glucose monitors from being covered under durable medical equipment to now being billed at the pharmacy point of sale. These changes include updates to the diabetic supply policy and MSM Chapter 1200, the pharmacy services billing manual and the diabetic supply link and the Nevada Medicaid website. The DHCFP has established a list of preferred products including the Dexcom kit and Freestyle Libre and the Omnipod system. This will help the state to with diabetic supply expenditures without negatively affecting the quality and access to care.

Jennifer Wheeler, Chair: For clinical presentation, we have a possible call to action on the multiple sclerosis agents.

Holly Long: Before we start, I want to introduce our new DUR Board member, Jessica Cate. She is a pharmacist, currently practicing at the Veteran Affairs Health Care System. Welcome, we appreciate you being here. I also want to welcome our new chair, Jen Wheeler and our new vice-chair Neto Adeolokun.

2. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for multiple sclerosis (MS) agents.

Carl Jeffery: The MS agents is a new class I am bringing to the Board to add PA criteria. We do have existing criteria for Ampyra, that is the only agent called out. There have been some new medication and not all are the same as others. So we just want to add some controls so we are pushing people to the safer agents. This starts on Page 36. There is the proposed criteria. Most medications fall in the first category and are the safest. Some of the less safe agents have their own criteria. The main criteria is a diagnosis of relapsing remitting or secondary progressive MS. There is criteria for Zinbryta, but it has been pulled from the market. Lemtrada, Mavenclad and Ocrevus have specific criteria in their indication for safety. There are several pages of criteria. The utilization on Page 44, it is pretty steady.

Jennifer Wheeler, Chair: Are we going to take out Zinbryta?

Carl Jeffery: It does not hurt to leave it in there just in case.

Jennifer Wheeler, Chair: Is there any public comment on this class? Any opposition from the Board? Is there any input from the MCO's?

Ryan Bitton: We are fine with the criteria. We had a requirement to be a specialist like neurologist or a specialist in MS.

Jennifer Wheeler, Chair: So diagnosis has to come from a specialist.

Tom Beranek: We also have age over 18 years old. We have a max dose of two tabs per day, 10 per cycle and two cycles per course and one course per year for Mavenclad.

Lisa Todd: I do not have anything to add for Anthem. One thing on our data that I noted was that Ocrevus numbers a low because we had six members with eight claims, but Ocrevus is usually covered on the medical side. But we do have a few pharmacies that are supplying the medication to the facility. We did not have any claims for Mavenclad.

Jennifer Wheeler, Chair: If there is no opposition, can we move to vote?

Motion to accept the criteria as presented by Optum. Second. The motion carries.

b. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Zelnorm (tegaserod).

Jennifer Wheeler, Chair: The next medication is Zelnorm. Is there anyone here to speak?

Carl Jeffery: Zelnorm is back on the market, it was pulled for safety concerns, but it has come back with more restrictions. It is indicated for IBS-C for women less than 65 years of age. The proposed criteria mirrors the indication, they have an indication of IBS-C, the member is female, less than 65 years and trial or contraindication to lactulose or polyethylene glycol. This would be included with the other IBS agents.

Jennifer Wheeler, Chair: Ryan, do you want to present?

Ryan Bitton: We do not have any additional recommendations.

Tom Beranek: We have a max of 12 mg or two tabs per day and limited to 12 months.

Lisa Todd: Anthem does not have anything.

Jennifer Wheeler, Chair: Any comments from the Board?

Carl Jeffery: Looking at utilization, Linzess really is the only one, a little Viberzi. We do not have a lot of utilization in this class anyway.

Tom Beranek: Our utilization almost mirrors fee-for-service. No real high volume.

Ryan Bitton: From HPN, our preferred agent is Trulance, so it has more utilization.

Lisa Todd: Anthem's data mirrors fee-for-service.

Jennifer Wheeler, Chair: Can I get a motion to adopt the criteria?

Motion to accept the criteria as presented by Optum, and second. Voting, Ayes are unanimous, the motion carries.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for monoclonal antibody agents.

Jennifer Wheeler, Chair: The next on the list is the monoclonal antibodies. This is on Page 112 in the binder. For Nucala, do we have anyone in the audience to speak on behalf of this drug? On the phone?

Carl Jeffery: Nucala, we have criteria already, but it is only for asthma. It has an updated indication for eosinophilic granulomatosis with polyangiitis. We wanted to include the diagnosis. The other new drug is Dupixent. That criteria starts on Page 106. It is similar indication for asthma and atopic dermatitis and chronic rhinosinusitis with nasal polyposis. This was included with the immunomodulators because of the atopic dermatitis, but it does belong in this class. The criteria mirrors the other agents. The diagnosis, the age and the other criteria with the indication. We do have some utilization data.

Holly Long: Just to clarify, the proposed criteria is to add the new indication for Nucala current policy and then to also add Dupixent with the proposed criteria.

Carl Jeffery: The fee-for-service utilization is dominated by Xolair followed by Dupixent. Cinqair is given in the doctor's office, so we may not see the claims in our data.

Jennifer Wheeler, Chair: On the package insert for Nucala, they recently changed the age to six. Should we change that now? It does not look like it is specific for the new indication.

Carl Jeffery: Yes, it will save us from having to bring it back. We will change the age from 12 to six.

Jennifer Wheeler, Chair: Severe asthma ages six to 11 it is a 40mg dose every 4 weeks, severe asthma in ages 12 and over is 100mg dose. That is very new.

Holly Long: We can do updates for FDA indications, but this is easier.

Jennifer Wheeler, Chair: Do the MCO's have anything different or in addition?

Ryan Bitton: For EGVA, we have a requirement of a history of asthma and the presence of two symptoms to verify the diagnosis. That was our recommendation.

Tom Beranek: We have a max dose of 300 mg every four weeks.

Lisa Todd: For Anthem for Dupixent, we have some additional treatments and failures language for atopic dermatitis. The member must have the phototherapy has failed to maintain remission or is contraindicated. Along with that, two of the following: 1. Intolerance to treatment; 2. Hypersensitivity reactions; 3. significant atrophy; 4. Is systemic effects.

Jennifer Wheeler, Chair: Any comments from the board? We will change from 12 years to six years or older for the indication, we will vote on approving the criteria as presented by Optum.

Motion and second. Voting: Ayes across the board, the motion carries.

d. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Nayzilam (midazolam).

Jennifer Wheeler, Chair: The next item is the midazolam. Anyone in the audience for public comment? Anyone on the phone?

Carl Jeffery: This is a unique indication and there are some other agents coming out too. The nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older. Our criteria includes the diagnosis, member is 12 years and specific dose limits. The dose limited to not exceed two sprays per seizure cluster and no more than one episode every three days and no more than five episodes per month. We would just put the quantity limit. But no other restrictions. The renewal would just be a positive clinical response. Looking at utilization, this is a new product and was not available when we ran the reports. Clonazepam is the highest use followed by the generic Onfi. Not a whole lot of use in this category. We do not know if Clonazepam is being used for seizures here.

Ryan Bitton: We are good with the criteria.

Tom Beranek: We recommended adding the recipient is currently on a stable regimen of anti-epileptic drugs. We did not have any utilization of this.

Lisa Todd: Anthem agrees with the criteria as presented and we did not have any utilization.

Jennifer Wheeler, Chair: Any comments from the board?

Brian Le: Do we need to add some restriction for people on multiple benzodiazepines?

Carl Jeffery: I am not familiar enough with this, should they not be on Onfi and midazolam?

Brian Le: Midazolam is an anesthetic drug commonly used for anesthesia. The concern I have is that more people will come in on a benzo with amnesia. We may get into problems. I see some people come with two or three benzos.

Beth Slamowitz: Would that be addressed with the pro-DUR edit?

Carl Jeffery: It would be, but the pharmacist would be able to override the denial. We would want some language for the call center to review for multiple benzos. If the system is set to deny for two benzos, we would need some policy to back it up.

Dave England: I concur with Dr. Le, if they have more than one, my guess with the nasal spray, what is the abuse potential. For the indication, if they have used two sprays and they are still having a seizure, what is to stop them from using another? I would like to see more criteria for what else they can use this with. This is used for emergency, not maintenance.

Brian Le: Nasal sprays act much faster than oral, but I am not sure midazolam works that much better for seizure.

Carl Jeffery: That is why we are putting the criteria in with the specific diagnosis, to limit the use. There are more products like this coming out, so we will see it again.

Beth Slamowitz: We suggesting this as a class?

Carl Jeffery: No, this is just for Nayzilam.

Beth Slamowitz: We do have anticonvulsants.

Carl Jeffery: Right, for children.

Beth Slamowitz: We already have PA criteria, does it make sense to put it under that class?

Jennifer Wheeler, Chair: So, placing it under which class?

Beth Slamowitz: Its main use is for an anticonvulsant, so it would be under that class and the criteria would apply. What do you think from a call center perspective?

Carl Jeffery: If we just apply to the current anticonvulsant, the criteria would only apply to children, but it would not apply to adults.

Beth Slamowitz: For adults, it would have to have a Pro-DUR edit. What kind of lookback does the call center do?

Carl Jeffery: They can do whatever we ask.

Beth Slamowitz: If we want them to look back three or six months, we would need that in criteria.

Jennifer Wheeler, Chair: Does anyone have any suggested look-back time-frame?

Beth Slamowitz: I think 30 days would be sufficient.

Carl Jeffery: Let me clarify, we are going to add a criteria that says anybody who is on concurrent benzodiazepine within 30 days of the request will not be approved.

Brian Le: I'm just concerned about benzo and opiate, because a lot will be on an opiate too. Can we require a specialist review?

Beth Slamowitz: That is why I think a hard-stop Pro-DUR edit to require the pharmacist to notify the prescriber about the concurrent benzos.

Brian Le: And with an opiate.

Beth Slamowitz: We already have that with the SUPPORT act required that edit.

Carl Jeffery: You're talking about a soft edit, something that the pharmacist can override at the pharmacy. A hard edit is something that cannot be bypassed.

Beth Slamowitz: Right, I don't want them to override the edit without…

Carl Jeffery: With a hard edit, the physician would have to call the PA call center for the override.

Beth Slamowitz: So it depends on how specific you want to get. It is not going to be a pharmacist doing the assessment at the call center. I do not know if that is something that can be escalated or if we need some criteria spelled out.

Carl Jeffery: There are soft edits already to warn dispensing pharmacists that they are on multiple or duplicate therapies. The package insert says there is nothing that contraindicates use with another benzo. Using two central nervous system depressants would cause the Pro-DUR edit to prompt the pharmacist to review. They would have to reach out the physician if appropriate. The Nayzilam would have a PA requirement already if we pass this.

Dave England: One question I have, it comes as a package of two per dose, the criteria says the dose will not exceed two per seizure cluster and no more than one episode every three days and treat no more than five episodes per month. So, does that mean we would allow the patient to be taking 10 packages.

Netochi Adeolokun: Since this is a new class of drugs, could we add that it be prescribed by a neurologist? That might fix some of the issues they are not on another benzo or opioid?

Brian Le: When a patient comes in, we do not often see the full list of medications. The primary care doctor is the best way to get the full list of medications. The call center would be able to see if the member is on other CNS depressants. If we leave it to a specialist, they may not see the full list.

Jennifer Wheeler, Chair: In Nevada, they are expected to review the PMP, so they should see if they are on other medications. And they would still have the DUR edits for duplication of therapy.

Brian Le: I think that is good.

Jennifer Wheeler, Chair: Would you like to add the neurologist requirement?

Carl Jeffery: It is my thought that this level of seizure is so complex and specific that it would have to be at least diagnosed by a neurologist. I think at that point you can say prescribed by or in consultation with a neurologist.

Dave England: I think that is the best way to put it.

Jennifer Wheeler, Chair: So we are going to add to the criteria prescribed by or in consultation with a neurologist for Nayzilam.

Motion to accept, seconded. Voting: Ayes are unanimous, the motion carries.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for narcolepsy agents.

Jennifer Wheeler, Chair: The next we have is Sunosi. Do we have any public comment?

Gary Phillips: I am Gary Phillips, I am the medical science liaison with Jazz pharmaceuticals. I want to make some comments about the narcolepsy agents. Sunosi was approved in March 2019 for the indication of excessive daytime sleepiness and is available in scored 75mg tablets, 150mg tablets, dosed daily in the morning. Sunosi is not indicated to treat obstruction. Sunosi has a novel mechanism of action with binding activing at the dopamine and norepinephrine transporters. Covers side effects and clinical studies and warnings and precautions. Xyrem is indicated for the treatment of excessive daytime sleepiness and patients seven years and older. Covers REMS programs, adverse reactions and contraindications.

Carl Jeffery: We brought this to the last meeting and postponed because there were some disagreements of how narcolepsy is defined. I brought the same criteria back. I think what I presented last time was appropriate. It is indicated for narcolepsy and obstructive sleep apnea. The other three agents are already included, this would just add Sunosi to the criteria. The criteria would have the indication requirement, a trial and failure of other agents and then the renewal would be documentation of a positive clinical response. Looking at utilization, there is a downward trend overall, modafinil and Provigil are decreasing, we really don't see Xyrem used.

Ryan Bitton: We are good with the diagnosis and terminology and the step. I think the criteria requiring both modafinil and armodafinil, they are kind of the same drug. We tweak it a little, we have armodafinil and then on narcolepsy, we have a stimulant, amphetamine or methylphenidate and armodafinil.

Tom Beranek: We agree with fee-for-service, we did not have any utilization.

Lisa Todd: We agree with the criteria and there were no claims for Sunosi.

Jennifer Wheeler, Chair: Anyone from the board?

Jim Tran: I have a concern about the increase in heart rate. Can we exclude the patients with cardiovascular problems?

Jennifer Wheeler, Chair: Do you have any recommendations on how you would word that?

Jessica Cate: There is a warning and precaution that talks about blood pressure and heart rate increase.

Jennifer Wheeler, Chair: I see dose dependent.

Carl Jeffery: In the past the board has opted to add some language so the prescriber realizes there is cardiovascular risk and they are doing their due diligence on their side. So maybe something as simple as the prescriber has assessed for cardiovascular disease and serious heart problems.

Dave England: When they did the testing for the FDA, where there any issues in the studies?

Homa Woodrum: We really can't interact with the public like that.

Dave England: Where there other issues that identified patients that should specifically not get this medication. Are there specific indications that we should include in the criteria?

Beth Slamowitz: I think from a policy creation, we have to stick with FDA indications or contraindications. Allowing the physician to attest to the fact that they have done their due diligence with an overall health assessment. The attestation is what we can do to apply the policy.

Jennifer Wheeler, Chair: Is there anything on the Provigil or modafinil? They have similar warnings, so we would have to change it for all. There is a difference between a warning and contraindication.

Netochi Adeolokun: There is a contraindication for concomitant use within 14 days of MOAI, I'm not sure if that is something we want to add. The patient has been off MOAI's for 14 days.

Beth Slamowitz: Can we add an attestation that they are following the prescribing practices.

Carl Jeffery: We do not list every contraindication for every PA. I'm not sure we want to set that precedence.

Beth Slamowitz: It is a given that they should be following the prescribing guidelines. It is stated at the beginning of the Chapter 1200 that they need to prescribe according the FDA guidelines. Usually contraindications like that would be a contraindication that would come through the Pro-DUR edits and the pharmacist would have to evaluate. It would be on the provider's expertise at that time.

Holly Long: We can put in the specific language in the criteria, we can make an overall statement or we can add an overarching statement to cover everything.

Dave England: I think unless there is something like a very serious adverse event or death, I think we are doing our due diligence.

Beth Slamowitz: I think the pharmacist would share some of the liability. From our perspective from utilization that what is prescribed is safe and effective.

Jennifer Wheeler, Chair: Can I get a motion to vote for the original criteria as Optum presented?

Motion and second. Voting: Ayes are unanimous, the motion carries.

3. Public Comment on any DUR Board Requested Report

4. DUR Board Requested Reports

Jennifer Wheeler, Chair: Next we have our standard reports for the board. Are there any public comments on the reports? The first is the opioid utilization top prescribers and members. Page 190.

Dave England: This is the actual count of members, not morphine equivalent dose.

Carl Jeffery: On Page 190 for fee-for-service, it has two graphs. The bottom shows the morphine equivalent dose. That is the one where you see the trend over the months. The top is how we have been looking at in the past to compare. We are still seeing a significant drop in the number of claims. Also, since we included the morphine equivalent dose, we see a decrease in that one as well.

Dave England: I was looking at the facility I have been working, the sum of equivalent dose, but if we divide out by patient, we can get how many per patient. The CDC says anything over 20 is dangerous. I'm curious what our MME per patient per day?

Carl Jeffery: I can add that field for the next report.

Dave England: It is just what the CDC pushes.

Brian Le: I did some quick calculations, our average would change completely because some doctors would be higher. The first one is about 57. The number five is more than 100mg per day.

Dave England: That is where the problems could be. We may have a few people using higher doses. I have not seen a great algorithm of where we should go when cutting down opioids. We push NSAIDs, but then we see more bleeding. How do you keep people comfortable?

Brian Le: The third member, that dose is really high.

Jennifer Wheeler, Chair: What is our intervention looking at these.

Holly Long: I would consider waiting for the next meeting with the additional information Dave is talking about. We could consider sending out another letter for information and education.

Brian Le: For the third member on methadone, they should be seen by the psychologist for the use of opioid. If they are using for addiction, it is probably ok, but for pain it is not appropriate.

Carl Jeffery: We cannot see why they are using it. There may be some interventions we can do with some specific patients to encourage Suboxone type therapy.

Dave England: Is this methadone for analgesia or rehab? That is going to guide our recommendation.

Beth Slamowitz: If methadone is being used for pain, it should be coming from a clinic. So we could look at place of service to see if it is being used for pain vs. opioid treatment. I wonder if there is an option for a retro-DUR for a MME per patient and then sending letters to prescribers over a certain number. We could ask for a response of what they are treating with the methadone.

Brian Le: Can we run a report with ICD?

Beth Slamowitz: Unless we require that through the point of sale, we do not have that information. Even if we look at the medical data, we see the last ten ICD's. If they come to an emergency room, they may have five diagnoses listed and they may not be treated for all of them at the emergency room.

Dave England: This is good data though, it shows we are going in the right direction.

Holly Long: Would you like us to bring back next time?

Dave England: Yes, I'm interested in seeing the per patient.

Carl Jeffery: And then sort the prescribers by count of patients and MME's.

Lisa Todd: Which chart are we adding these to?

Holly Long: We are going to add the average MME per patient per day to the existing charts. And then sorting prescribers by…

Carl Jeffery: My thought is we would take the top ten prescribers, divide the MME by the number of members by the days' supply to get the average, it would be a calculated field. We could do it now. The top ten is going to look different, I think it will give us some good information. From there we can address the top ten prescribers for another retro-DUR activity.

Jim Tran: Is there any way to pull naloxone?

Carl Jeffery: You mean like the emergency use? We looked at that a few meetings ago. There was not much use. We do not know if people are actually using it or just filling it to have at home for emergency use.

Beth Slamowitz: The Department of Public and Behavior Health has a lot of that data posted on their website.

Ryan Bitton: HPN is seeing the same trend. We have benzos in here as well. The benzo and total MME and total scripts are all decreasing.

Holly Long: Have any of you run the data like we are talking about?

Ryan Bitton: We have run lots of reports, but I am not sure we have done the same thing. We put everything through prior authorization if over 90 MME.

Beth Slamowitz: You might get some trend information. If you see the same prescriber all the time that is prescribing over the allowed amount, it might be worth to put that prescriber on point.

Dave England: It is important to look at the type of practice with the high numbers where if they are ortho or pain management.

Tom Beranek: We are seeing the same trend month over month. There is a nice downward trend. The top ten prescribers are the same every month. The pain management is usually at the top.

Lisa Todd: We are about the same. Our opioid utilization is going down from the beginning of the time period. It was about 300 fewer member received opioids from October to September, the claim counts went down by about 500. Our top opioid prescribers, we are seeing the same prescribers quarter after quarter, they do not move much in the rank.

Carl Jeffery: The benzo report is on Page 194. The top report is the number of utilizing members. This is from the top ten opioid utilizing member and if they are on any benzos. Two of the members do not have any benzos. This does not concern me much. The next report is looking at prescribers, our number one opioid prescriber does not write for much benzo, just hydroxyzine which falls as an anxiolytic. The other prescribers do not have too many claims either. Two of the prescribers did not even prescribe any benzo at all.

Ryan Bitton: Similar, nothing really concerning. None of our top ten opioid prescribers are part of our top benzo prescribers. We do not see overlap. We did see one of our top members get a lot of benzos. We found many of the top opioid prescribers do not write for benzos.

Tom Beranek: SilverSummit is similar. I do have two prescribers showing in the top ten opioid in the top benzo prescribers. One is an anesthesiologist and the other is psychiatry. The trend is going down similar to the opioids. Those that write for both, we see the opioid prescription is for MAT and the benzo to go with it.

Lisa Todd: For Anthem, we are very similar. None of the top opioid providers were in the top benzo providers. There were three providers on the top ten opioid prescribers that hit the top 25 members receiving benzos. I compared the benzos and opioids together, it was interesting, I broke it out by second and third quarter with benzos and opioids together. There is a down-trend of members who have received benzos and opioids from second to third quarter.

5. Public Comment on any Standard DUR Report

6. Standard DUR Reports

Jennifer Wheeler, Chair: Any public comment on the standard DUR reports?

Carl Jeffery: Page 196 is where the standard reports start. Anti-hemophilia is still our top. Anticonvulsants are surprising, they are about $500,000 in quarter three vs. quarter two, this is because of Lyrica going generic. Everything else is as expected. The opioids on the bottom by claim count, the opioids were the top for several months, but now the anticonvulsants have taken over, and then the sympathomimetics are your products like albuterol inhalers.

Ryan Bitton: From HPN, most of the Q2 vs. Q3 stays the same from paid and claim count perspective. Nothing concerning.

Tom Beranek: Ours is a little different in that anticonvulsants are not as high. The MS agents are dropping. The SGLT2 are jumping in. For us it is antiretrovirals, sympathomimetics and insulins are the big cost drivers for SilverSummit.

Lisa Todd: For Anthem, our data is a little different. The quarters are consistent with drug classes. Our biggest cost drivers are antiretrovirals and anti-TNF, sympathomimetics are up there as well.

Carl Jeffery: The next is the pro-DUR chart. There is a lot of data to present on this report. You can see the paid, rejected and reversed for the different claims. On the chart below, you see the specific edits, how many paid, rejected and how many reversed and how many were eventually filled. The next page shows the details for what is exactly in each of the edits on the first page. Nothing I need to call out, everything is standard and expected.

Ryan Bitton: From HPN, we have similar data, nothing really to call out.

Tom Beranek: SilverSummit, we have two or three of the edits that really drive the trends. Albuterol and gabapentin and metformin usually show up. Pretty similar to what other programs are seeing. Nothing really to call out. We do see a lot of overrides for therapeutic duplication.

Lisa Todd: For Anthem, I would like to say our data is the same, but it is not. I do have a note that our pro-DUR edits were softer because we transitioned to a new PBM and after we went live, we realized the hierarchy logic for the rejects was different than what we had previously. We pulled this back to make sure folks could get their medications, but they have been re-initiated now. Normally our higher edits are early refill and therapeutic duplication. We have a whopping huge unknown.

Carl Jeffery: The last page on the fee-for-service is the retro-DUR. I will ask for feedback from the board, if you see something that we should address, please let us know. We are always willing to listen to ideas. What we reviewed was diabetes without statins, two or more long acting opioids and albuterol without a long-term control and high dose ADHD medications. If there is something you see in your practice, I appreciate getting that input.

7. Closing Discussion

a. Public comments on any subject.

Jennifer Wheeler, Chair: Do we have any public comments on anything we discussed today?

Sandy Sierawski: My name is Sandy Sierawski, I work for Pfizer here in Nevada. One of the topics I just wanted to bring up and maybe ask a couple questions or at least address to the committee is that during the last DUR meeting, one of the physicians sent in a letter requesting that the criteria for smoking cessation products be reviewed. And that comes from the idea of having consistent criteria between fee-for-service and the MCO's. I know you set the criteria for fee-for-service patients. You involve the MCO's for the process. Is there a process to make the criteria consistent? Or does the MCO's still make their own criteria?

Holly Long: Currently we are doing our own. The fee-for-service and each of the MCO's have their own criteria. It is in statute that they cannot have more stringent criteria.

Sandy Sierawski: How is the follow-up done. If you identify criteria and their criteria is more stringent…

Holly Long: They would have to change it. If we see something more stringent, then something needs to be updated. Sometimes they will let us know that they are changing so it is not more stringent. Is there something specific?

Sandy Sierawski: Yes, fee-for-service just has a quantity limit set, there is not a step edit, you do not have to try other meds to get other products. With the MCO's there is a step process, so therefore it is different and confusing to providers and patients.

Holly Long: If it is something that has not yet come to the DUR Board since we started collaboration, it might not be aligned. It was a go-forward change.

Beth Slamowitz: Something like step therapy, a lot of times they will address things through their PDL rather than prior auth. They may not be more stringent as far as the prior auth criteria, but they are allowed to set their own preferred drug list. Often that is where that comes in play. We do not address the preferred drug list here. We only address prior auth criteria here and from that standpoint, they cannot be more stringent. If it is a specific product, you can reach out to the MCO's so they can address internally.

b. Date and location of the next meeting.

Jennifer Wheeler, Chair: Is there any other public comment on any subject? The date and location of the next meeting will be April 30 at 1pm at the same location. The meeting is adjourned.

c. Adjournment.

Meeting adjourned 3:03 PM.

Clinical Presentations

Prior Authorization Guideline

Guideline Name	CGRP Inhibitors

1 . Indications

Drug Name: Ubrelvy (ubrogepant)
Migraine Indicated for the acute treatment of migraine with or without aura in adults
Drug Name: Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm)
Migraine Indicated for the preventive treatment of migraine in adults.
Drug Name: Emgality (galcanezumab-gnlm)
Migraine Indicated for the preventive treatment of migraine in adults. **Episodic Cluster Headache** Indicated for the treatment of episodic cluster headache in adults.

2 . Criteria

Product Name: Ubrelvy	
Diagnosis	Migraines
Approval Length	6 Months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of acute migraine with or without aura

AND

2 - Patient is 18 years of age or older

AND

3 – The prescribed dose will not exceed two doses per migraine episode and treating no more than 8 migraine episodes per 30 days.

AND

4 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

Product Name: Ubrelvy	
Diagnosis	Migraines
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has experienced a positive response to therapy

AND

2 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

Product Name: Aimovig, Ajovy or Emgality

Diagnosis	Migraines
Approval Length	6 Months [E]
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following:

1.1 Both of the following:

1.1.1 Diagnosis of episodic migraines

AND

1.1.2 Patient has 4 to 14 migraine days per month, but no more than 14 headache days per month [A, B, C]

or

1.2 All of the following:

1.2.1 Diagnosis of chronic migraines

AND

1.2.2 Patient has greater than or equal to 15 headache days per month, of which at least 8 must be migraine days for at least 3 months [A]

AND

1.2.3 Medication overuse headache has been considered and potentially offending medication(s) have been discontinued [I]

AND

2 - Patient is 18 years of age or older [J]

AND

3 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

AND

4 - Two of the following [D, E, F, G, H, 10]:

4.1 One of the following:

- History of failure (after at least a two month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- Patient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

or

4.2 One of the following:

- History of failure (after at least a two month trial) or intolerance to Depakote/Depakote ER (divalproex sodium) or Topamax (topiramate)
- Patient has a contraindication to both Depakote/Depakote ER (divalproex sodium) and Topamax (topiramate)

or

4.3 One of the following:

- History of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol, or metoprolol
- Patient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol, or metoprolol

Product Name: Aimovig, Ajovy, or Emgality	
Diagnosis	Migraines
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - Use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy

AND

3 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

AND

4 - For Chronic Migraine only: Patient continues to be monitored for medication overuse headache (MOH) [I]

Product Name: Emgality	
Diagnosis	Episodic Cluster Headaches
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of episodic cluster headache

AND

2 - Patient has experienced at least 2 cluster periods lasting from 7 days to 365 days, separated by pain-free periods lasting at least three months [21]

AND

3 - Patient is 18 years of age or older [J]

AND

4 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

Product Name: Emgality	
Diagnosis	Episodic Cluster Headaches
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist

3 . Endnotes

A. The International Classification of Headache Disorders, 3rd addition (beta version) distinguishes chronic and episodic migraine [11]. Chronic migraine is described as headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month. Episodic migraine is not clearly defined, but is applied when a patient is diagnosed with migraine but does not meet criteria for chronic migraine.

B. While every patient with chronic migraine should receive preventive therapy, not every patient with episodic migraine needs prevention [12]. Appropriate candidates for preventative treatment include those with at least 4 days per month of headache-related disability.

C. The phase 3 inclusion criteria for the erenumab (LIBERTY, STRIVE, ARISE) and galcanezumab (EVOLVE-1, EVOLVE-2) pivotal trials in episodic migraine required that patients had 4 to 14 migraine days per month [3-9]. The LEADER trial evaluated patients who had failed two to four prior preventive migraine treatments (PMTs). At the start of the trial, 38.6%, 37.8%, and 22.8% of patients had failed two, three, and four prior PMTs, respectively [2].

D. The American Academy of Neurology supports the use of the following medications for the prevention of episodic migraine in adult patients (with level A or B evidence): antidepressants [i.e., Elavil (amitriptyline), Effexor (venlafaxine)], antiepileptics [i.e., Depakote/Depakote ER (divalproex sodium), Topamax (topiramate)], and beta-blockers [i.e., atenolol, propranolol, nadolol, timolol, metoprolol] [16]. They also support the use of Botox (onabotulinumtoxin A) as an efficacious treatment option for chronic migraine.

Botox (onabotulinumtoxin A) is not however recommended for episodic migraine treatment.

E. The US Headache Consortium Consensus (Table e-1) recommends that therapy be initiated with medications that have the highest level of evidence-based therapy while also taking into account patient specific comorbidities [15]. Each medication should be given an adequate trial, it may take two to three months to achieve clinical benefit, and six months to achieve maximal benefit.
F. The OptumRx clinical team consulted with a neurologist on the prospective review of the CGPR Inhibitors [14]. He confirmed that preventative treatment for chronic migraine and episodic migraine are similar. The choice of preventative medication will not vary much between the episodic vs chronic subtypes. The choice of agent will largely depend more on patient specific factors. Also, he felt that this agent will most likely fall into a similar place in therapy as Botox (onabotulinumtoxin A).
G. The National Institute for Health and Care Excellence guidelines for the management of migraine recommend Botox (onabotulinumtoxin A) as an option in chronic migraine after failure of at least three other prophylactic medications and that the patient is being managed for medication overuse [13].
H. The phase 2 chronic migraine trial for erenumab included patients who had failed up to three medication categories [17]. The most frequently used prior therapies in the chronic migraine trial were topiramate (68.3% of subjects), beta blockers (52.8%), and tricyclic antidepressants (48.2%) [18].
I. Medication overuse headache (MOH) is defined as headache occurring greater than or equal to 15 days per month. It develops as a consequence of regular overuse of acute or symptomatic headache medication for more than 3 months [11]. Current evidence suggests the best treatment strategy is withdrawal of the offending medication.
J. The safety and effectiveness in pediatric patients has not been established [1, 19, 20, 22].

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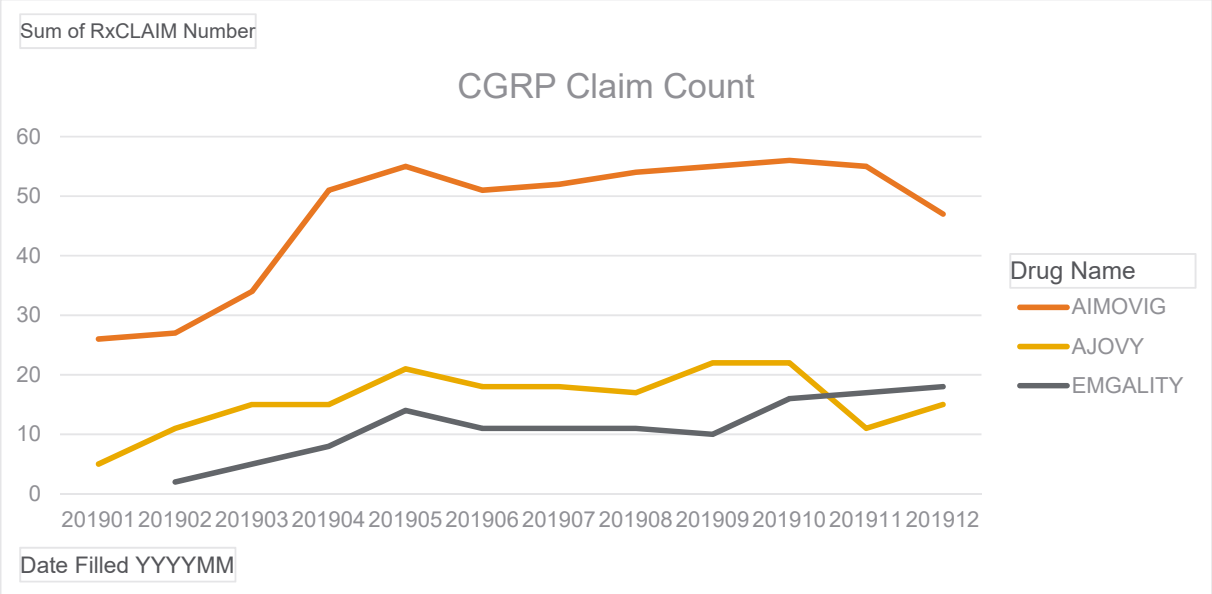
Nevada Medicaid

CGRP Agents
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
AJOVY	36	190	5881	303
EMGALITY	32	123	3938	138
AIMOVIG	106	563	18175	756



S. Anti-Migraine Medications

Therapeutic Class: Serotonin 5-HT1 receptor agonists (triptans)
Last Reviewed by the DUR Board: July 25, 2019

Therapeutic Class: Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications
Last Reviewed by the DUR Board: October 18, 2018

Serotonin 5-HT1 receptor agonists commonly referred to as "triptans" and CGRP Receptor Inhibitor medications or anti-migraine medications are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

Serotonin 5-HT1 Receptor Agonists (triptans)

1. Coverage and Limitations

An approved prior authorization is required for any prescription exceeding the quantity limits. Approval for additional medication beyond these limits will be considered only under the following circumstances:

a. The recipient's current medication history documents the use of prophylactic medications for migraine headache or the medical provider agrees to initiate such therapy which includes beta-blockers, tricyclic antidepressants, anticonvulsants, Selective Serotonin Reuptake Inhibitors (SSRIs) and/or calcium channel blockers; or

b. The medical provider is aware of and understands the implications of daily use and/or overuse of triptans and agrees to counsel the patient on this issue in an effort to taper the quantity of triptan medication required monthly.

1. Recipient's current medication history must NOT have Monoamine Oxidase (MAO) Inhibitors present for approval of Imitrex® (sumitriptan), Maxalt® (rizatriptan) or Zomig® (zolmitriptan).

2. Recipients whose current medication history indicates the use of propranolol will NOT be granted prior authorization of Maxalt® (rizatriptan) 10mg tablet or 10mg orally disintegrating tablet.

3. Prior authorization will NOT be given to patients with ischemic heart disease.

Approval for exceeding the quantity limits on tripitans will be given for a two month time period.

2. Prior Authorization Guidelines

The prior authorization must be initiated by the prescriber. The approved prior authorization must be available if requested.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications

1. Coverage and Limitations

a. Approval will be given if the following criteria are met and documented:

Episodic Migraines

1. Initial request:

a. The recipient must have a documented diagnosis of episodic migraines; and

b. The recipient must be 18 years of age or older; and

c. The recipient must have four to 14 migraine days per month, but no more than 14 headache days per month; and

d. One of the following:

1. The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil® (amitriptyline) or Effexor® (venlafaxine); or

2. The recipient has a contraindication to both Elavil® (amitriptyline) and Effexor® (venlafaxine); and

e. One of the following:

1. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote®/Depakote ER (divalproex) or Topamax® (topiramate); or

2. The recipient has a contraindication to both Depakote®/Depakote ER (divalproex) and Topamax® (topiramate); and

f. One of the following:

1. The recipient has a history of failure (after at least a two-month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol; or

2. The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol; and

g. The medication must not be used in combination with another CGRP Inhibitor.

Chronic Migraines

2. Initial request:

a. The recipient has a documented diagnosis of chronic migraines; and

b. The recipient must be 18 years of age or older; and

c. The recipient has been evaluated for medication overuse headache (MOH) and if the recipient is diagnosed with MOH, then treatment plan will include a taper off the offending medication; and

d. The recipient has ≥ 15 headache days per month, of which at least eight must be migraine days for at least three months; and

e. One of the following:

1. The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil® (amitriptyline) or Effexor® (venlafaxine); or

2. The recipient has a contraindication to both Elavil® (amitriptyline) and Effexor® (venlafaxine); and

f. One of the following:

1. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote®/Depakote ER (divalproex) or Topamax® (topiramate); or

2. The recipient has a contraindication to both Depakote®/Depakote ER (divalproex) and Topamax® (topiramate); and

g. One of the following:

1. The recipient has a history of failure (after at least a two-month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol; or

2. The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol; and

h. The medication will not be used in combination with another CGRP Inhibitor; and

i. The medication will not be used in combination with Botox (onabotulinumtoxinA).

2. Recertification Request:

a. The recipient must have documented positive clinical response to CGRP therapy; and

b. The use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy.

3. Prior Authorization Guidelines

a. Prior authorization approvals will be for:

1. Initial prior authorization approval: three months.

2. Recertification approval: 12 months.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 4 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms. Ubrogepant is the only oral CGRP inhibitor (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of

olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- Two investigational CGRP inhibitors with near-term anticipated approvals include rimegepant, an oral tablet and oral disintegrating tablet CGRP inhibitor, and eptinezumab, an IV formulation that could be funded under the medical benefit. Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	−
Ajovy (fremanezumab-vfrm)	−
Emgality (galcanezumab-gnlm)	−
Ubrelvy (ubrogepant)	−

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Ubrelvy** (ubrogepant)
Acute treatment of migraine with or without aura in adults	-	-	-	✔ *
Preventive treatment of migraine in adults	✔	✔	✔	-
Treatment of episodic cluster headache in adults	-	-	✔	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019, Ubrelvy 2019*)

- 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

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 open-label extension (OLE) trial in unpublished formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and

safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).

- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Erenumab-aooe

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD as approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the most bothersome symptom (MBS) freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days

(mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.

- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2019, Ubrelvy prescribing information 2019*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

        - Magnesium IV
        - Isometheptene compounds
        - Combination medications (codeine/APAP, tramadol/APAP)
        - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    - Ubrogepant was reviewed by the AHS prior to FDA-approval for recommendation. The AHS recommend it may have a role in patients with cardiovascular (CV) conditions or in cases of triptan contraindications. Further recommendations include patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
        - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
    - Level A (established efficacy and > 2 Class I trials):
        - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
        - Beta blockers: metoprolol, propranolol, and timolol
        - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
    - Level B (probably effective and 1 Class I or 2 Class II trials):
        - Antidepressants: amitriptyline and venlafaxine
        - Beta blockers: atenolol and nadolol
        - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
    - Level C (possibly effective and 1 Class II trial):
        - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
        - Angiotensin II receptor blockers (ARBs): candesartan
        - Alpha agonists: clonidine and guanfacine
        - Antiepileptic drugs: carbamazepine
        - Beta blockers: nebivolol and pindolol
        - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
    - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
    - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
    - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).

- Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. In cases of serious or severe reactions, treatment should be discontinued.
- Erenumab-aooe has an additional warning and precaution associated with constipation with serious complications noted post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- For the prevention of migraine, erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor prevention studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- For the treatment of episodic cluster headache, galcanezumab−gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- For the treatment of acute migraines, the safety of ubrogepant was evaluated for up to 1 year in an OLE in patients who had ≥ 2 attacks/month. The most common adverse events were nausea (2 to 4%) and somnolence (2 to 3%). The most common adverse reaction resulting in discontinuation in the OLE was nausea.

- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with the 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2019, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Episodic cluster headache: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Max dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Ubrogepant is indicated for acute treatment of migraine with or without aura. Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are indicated for the prevention of migraine. Galcanezumab−gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.

Recent AHS guidelines state that ubrogepant may have a role in patients with CV conditions or in cases of triptan contraindications. It is also noted that other CGRP inhibitors may shortly be FDA-approved for use.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, ubrogepant has a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions in SC formulations and nausea in oral formulations.
- Overall, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and ubrogepant is the only CGRP inhibitor indicated for acute treatment of migraines and also the only oral formulation. The frequency of administration (and route or dose) vary by indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal

	potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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Publication Date: January 2, 2020

Prior Authorization Guideline

Guideline Name	Cystic Fibrosis Agents

1 . Indications

Drug Name: Trikafta (elexacaftor/tezacaftor/ivacaftor)
Cystic Fibrosis Indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation.

2 . Criteria

Product Name: Trikafta	
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient is 12 years of age or older

AND

2 - Diagnosis of cystic fibrosis (CF)

AND

3 - Patient has at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene as detected by a FDA-cleared cystic fibrosis mutation test or a test performed at a Clinical Laboratory Improvement Amendments (CLIA)-approved facility

AND

4 - Prescribed by or in consultation with one of the following:

- Pulmonologist
- Specialist affiliated with a CF care center

Product Name: Trikafta	
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to Trikafta (elexacaftor/tezacaftor/ivacaftor) therapy (e.g., improvement in lung function [percent predicted forced expiratory volume in one second {PPFEV1}] or decreased number of pulmonary exacerbations) [1,2]

3 . References

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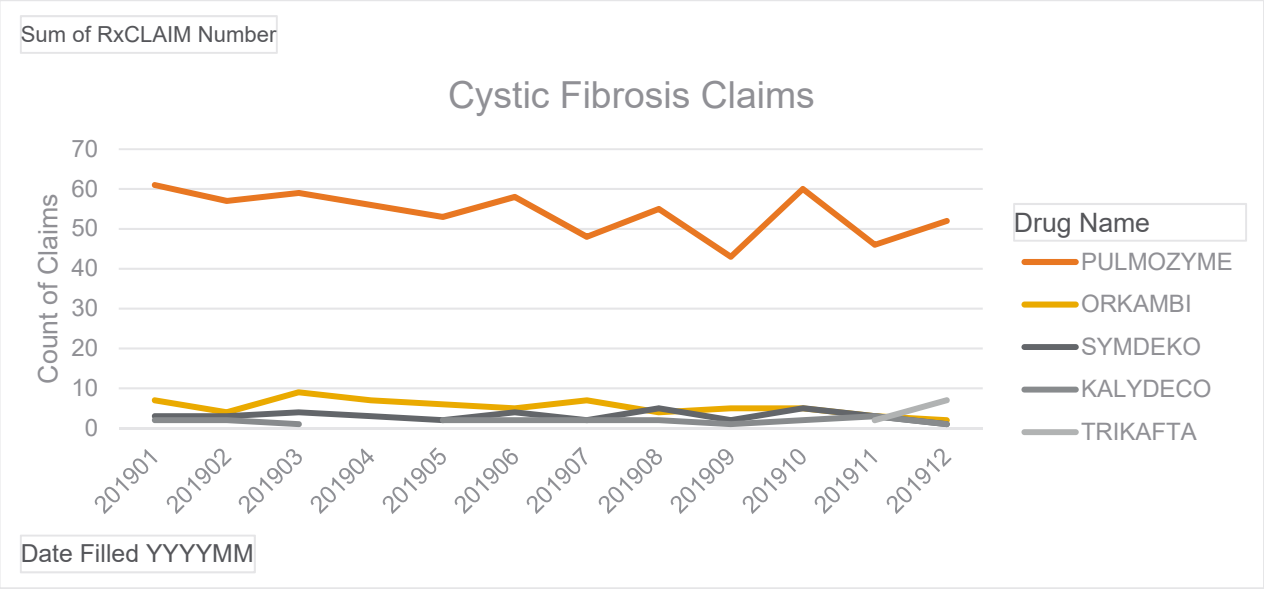
Nevada Medicaid

Cystic Fibrosis Agents

Fee for Service

January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
ORKAMBI	8	64	1,792	5,992
KALYDECO	3	20	560	1,120
SYMDEKO	6	37	1,036	2,072
TRIKAFTA	6	9	252	756
PULMOZYME	98	648	18,460	56,338



LL. Kalydeco® (ivacaftor)

Therapeutic Class: Cystic Fibrosis Agent
Last Reviewed by the DUR Board: July 26, 2018

Kalydeco® (ivacaftor) is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. The recipient is six months of age or older; and

   b. The recipient has a diagnosis of cystic fibrosis; and

   c. There is documentation that the recipient has had an FDA-approved cystic fibrosis mutation test confirming the presence of one of the gene mutations listed in the FDA-approved package insert; and

   d. The medication is prescribed by or in consultation with a pulmonologist or a specialist affiliated with a cystic fibrosis care center.

2. Recertification Request (the recipient must meet all the following criteria)

   a. Authorization for continued use shall be reviewed at least every 12 months when the following criteria are met:

      1. Documentation of a positive clinical response to Kalydeco® therapy.

3. Prior Authorization Guidelines

   a. Prior authorization approval will be for one year.

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

HHH. Orkambi® (lumacaftor/ivacaftor)

Therapeutic Class: Cystic Fibrosis Agent
Last Reviewed by the DUR Board: January 26, 2017
Previously reviewed November 5, 2015

Orkambi® (lumacaftor/ivacaftor) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. The recipient has a diagnosis of cystic fibrosis; and

   b. The recipient is two years of age or older; and

   c. The recipient is homozygous for the F508del mutation in the CFTR gene; and

   d. The requested dose is two tablets every 12 hours; or

   e. The requested dose is one tablet every 12 hours in the presence of severe hepatic impairment.

2. Prior Authorization Guidelines

   a. Prior authorization approvals will be for one year.

   b. Prior Authorizaition forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

VVV. Symdeko® (tezacaftor/ivacaftor)

Last Reviewed by the DUR Board: July 26, 2018

Symdeko® (tezacaftor/ivacaftor) is subject to prior authorization and quantity limits based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Initial Request:

1. The recipient is six years of age or older; and

2. The recipient has a documented diagnosis of cystic fibrosis (CF); and

3. The medication must be prescribed by or in consultation with one of the following:

a. Pulmonologist.

b. Specialist affiliated with a CF care center.

4. One of the following:

a. The recipient is homozygous for the F508del mutation as detected by an FDA cleared cystic fibrosis mutation test or Clinical Laboratory Improvement Amendments (CLIA) approved facility; or

b. The recipient has one of the FDA approved package insert listed mutations on at least one allele in the CF transmembrane conductance regulator (CFTR) gene as detected by FDA cleared cystic fibrosis mutation test or CLIA approved facility.

b. Recertification Request (the recipient must meet the following criteria):

1. Authorization for continued use shall be reviewed at least every 12 months when the following criteria is met:

a. Documentation of a positive clinical response to Symdeko® (tezacaftor/ivacaftor) therapy (e.g., improvement in lung function or decreased number of pulmonary exacerbations).

2. Prior Authorization Guidelines

a. Prior authorization approval will be given for 12 months.

b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators and dornase alfa

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 300 have been confirmed to cause CF (*CFTR2 2019*, *Quon and Rowe 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*). The most common *CFTR* mutation leading to CF is the *F508del* mutation; approximately 50% of patients with CF are homozygous for this mutation, and 90% carry at least 1 copy (*Katkin 2019*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon and Rowe 2016*).
  - Inhaled antibiotics have commonly been used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF. A reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, and oral macrolide antibiotics and high-dose ibuprofen have been used to reduce inflammation (*Quon and Rowe 2016*).
    - Pulmozyme (dornase alfa), initially approved by the Food and Drug Administration (FDA) in 1993, is a recombinant DNase enzyme. In CF patients, retention of viscous purulent secretions in the airways contributes to reduced pulmonary function and to exacerbations of infection. Dornase alfa hydrolyzes deoxyribonucleic acid (DNA) in the sputum of CF patients, reducing sputum viscoelasticity. Guidelines recommend the use of dornase alfa for patients with CF aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations) (*Drugs@FDA 2020, Mogayzel et al 2013*).
- More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) (*Drugs@FDA 2020, Elborn 2016*). The CFTR modulators facilitate processing and trafficking of CFTR to the cell surface (CFTR correctors [tezacaftor, lumacaftor, and elexacaftor]) or facilitate increased chloride transport at the cell surface (CFTR potentiator [ivacaftor]). Eligibility for CFTR modulator therapy depends on the patient's age and CF-causing mutation(s).
  - In 2018, prior to the approval of Trikafta and some age expansions for the other CFTR modulators, it was estimated that only 55% of patients with a known genotype were eligible for CFTR modulator therapy (*Vertex CF portfolio guide 2018*). The approval of Trikafta may provide the opportunity for up to 90% of CF patients to be eligible for CFTR modulator therapy in the future (*Vertex 2019*).
  - The CFTR modulators are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the 4 available CFTR modulators and dornase alfa.
- Medispan Class: CF Agents, CFTR Potentiators (Kalydeco); CF Agents, CF Agent-Combinations (Orkambi, Symdeko, and Trikafta); and CF Agents, Hydrolytic Enzymes (Pulmozyme)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
CFTR Modulators	
Kalydeco (ivacaftor)	-
Orkambi (lumacaftor/ivacaftor)	-

Drug	Generic Availability
Symdeko (tezacaftor/ivacaftor)	-
Trikafta (elexacaftor/tezacaftor/ivacaftor)	-
DNase enzyme	
Pulmozyme (dornase alfa)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	CFTR Modulators				DNase Enzyme
	Kalydeco (ivacaftor)	**Orkambi** (lumacaftor/ ivacaftor)	**Symdeko** (tezacaftor/ ivacaftor)	**Trikafta** (elexacaftor/ tezacaftor/ ivacaftor)	**Pulmozyme** (dornase alfa)
Treatment of CF in patients aged 6 months and older who have 1 mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data*	✔				
Treatment of CF in patients aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene		✔			
Treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in the *CFTR* gene that is responsive to tezacaftor/ ivacaftor based on *in vitro* data and/or clinical evidence†			✔		
Treatment of CF in patients aged 12 years and older who have at least 1 *F508del* mutation in the *CFTR* gene				✔	
For daily administration in conjunction with standard therapies for the management of CF patients to improve pulmonary function‡					✔

* The following 38 mutations are included: *E56K, P67L, R74W, D110E, D110H, R117C,* ***R117H***, ***G178R***, *E193K, L206W, R347H, R352Q, A455E,* ***S549N***, ***S549R***, ***G551D***, ***G551S***, *D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T,* ***G1069R***, ***R1070Q***, *R1070W, F1074L, D1152H,* ***G1244E***, ***S1251N***, ***S1255P***, *D1270N,* ***G1349D***, *2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: Bolded mutations are unique to the indication for Kalydeco and are not covered by another CFTR modulator.

† The following 27 mutations are included (patients must have 2 copies of the *F508del* mutation, or at least 1 copy of another listed medication, for Symdeko to be indicated): *E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, F508del, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: All of these mutations are also covered by either Kalydeco or Orkambi.

‡ In CF patients with a forced vital capacity (FVC) ≥ 40% of predicted, daily administration of dornase alfa has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

(*Prescribing information: Kalydeco 2019, Orkambi 2018, Pulmozyme 2018, Symdeko 2019, Trikafta 2019*)

- 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

CFTR Modulators

Note: The following is a brief overview of the clinical evidence supporting the efficacy of the CFTR modulators. Appendix A provides an overview of key clinical trials for CFTR modulators in a table format. Appendix B provides a description of study endpoints.

- The safety and efficacy of ivacaftor have been evaluated in a number of trials in patients with a variety of *CFTR* mutations. In addition to the clinical evidence available, ivacaftor has been FDA-approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 48-week, double-blind trial demonstrated improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and exacerbations for ivacaftor vs placebo in 167 patients with CF aged ≥ 12 years with ≥ 1 *G551D* mutation (*Ramsey et al 2011*). A separate, placebo-controlled, 48-week double-blind trial in 52 patients aged 6 to 11 years with this mutation demonstrated improvement in $ppFEV_1$ (*Davies et al 2013*), and an open-label extension study of these 2 trials demonstrated sustained $ppFEV_1$ improvement over 96 weeks (*McKone et al 2014*).
  - A placebo-controlled crossover trial with two 8-week treatment periods demonstrated improved $ppFEV_1$ with ivacaftor in 39 patients with CF aged ≥ 6 years with a non-*G551D* gating mutation (*De Boeck et al 2014*).
  - A 24-week, double-blind, placebo-controlled trial evaluated the safety and efficacy of ivacaftor vs placebo in 69 patients aged ≥ 6 years with an *R117H* mutation (*Moss et al 2015*). In this trial, improvement in $ppFEV_1$ was demonstrated in adults but not in children aged 6 to 11 years; the authors suggested that the lack of effect may have been related to the high baseline $ppFEV_1$ in the pediatric patients enrolled.
  - A crossover study with two 8-week treatment arms enrolled a total of 246 patients aged ≥ 12 years with CF who were heterozygous for *F508del* and a residual function mutation (*Rowe et al 2017*). A comparison of the ivacaftor and placebo arms demonstrated an improvement in $ppFEV_1$ with ivacaftor. (See the tezacaftor/ivacaftor section below for information on comparisons of tezacaftor/ivacaftor to ivacaftor and placebo in this study.)
  - An open-label study in 34 patients aged 2 to 5 years with CF and ≥ 1 *CFTR* gating mutation evaluated weight-based dosing of ivacaftor in this age group (*Davies et al 2016*). Patients weighing < 14 kg received a dose of 50 mg and those ≥ 14 kg received a dose of 75 mg. Pharmacokinetic analyses demonstrated that exposure was similar to that reported with the approved dosing in adults. Improvements were also seen in weight and sweat chloride concentrations (a pharmacodynamic endpoint that reflects changes in CFTR function). No meaningful data on lung function were available, as the accuracy of spirometry results is limited in this age group.
  - The efficacy of ivacaftor in patients aged 6 to < 24 months was extrapolated from data in patients aged ≥ 6 years with support from pharmacokinetic analyses showing similar drug exposure levels to adults. Safety of ivacaftor in this age group was derived from a cohort of 11 patients aged 6 months to < 12 months and a cohort of 19 patients aged 12 months to < 24 months in a 24-week, open-label study, which demonstrated that the safety profile was similar in this age group to that observed in patients aged ≥ 24 months. The study also demonstrated improvements in sweat chloride and markers of pancreatic function in patients aged 12 months to < 24 months (*Kalydeco prescribing information 2018, Rosenfeld et al 2018*).
  - A systematic review and meta-analysis evaluated the use of ivacaftor vs placebo in patients with CF (*Skilton et al 2019*). The review included 5 trials evaluating ivacaftor in patients with the *F508del* mutation (1 trial, N = 140), the *G551D* mutation (3 trials, N = 238), or the *R117H* mutation (1 trial, N = 69). Primary outcomes included survival, quality of life as assessed by the CF questionnaire-revised (CFQ-R), and FEV_1. Overall, the authors found evidence supporting the efficacy of ivacaftor in patients with the *G551D* mutation, but not the *F508del* or *R117H* mutations. Key findings from the review were as follows:
    - No survival data or deaths were reported in any of the included trials.
    - In studies of patients with the *F508del* mutation, no improvement was demonstrated in CFQ-R or FEV_1.
    - In studies of patients with the *G551D* mutation, improvement was demonstrated in both CFQ-R and FEV_1, although improvements in CFQ-R were not statistically significant at all time points.
    - In studies of patients with the *R117H* mutation, improvement was demonstrated in CFQ-R (in adults but not children), and there was no improvement in FEV_1.
  - Support for ivacaftor's efficacy for additional mutations is available from *in vitro* assay data (*Kalydeco prescribing information 2018*). This assay was based on CFTR chloride transport in Fisher Rat Thyroid cells expressing mutant

CFTR. An increase in chloride transport of ≥ 10% was designated as the response threshold because it is predictive or reasonably expected to predict clinical benefit. Mutations meeting this threshold were considered responsive, and a patient must have at least 1 responsive mutation in order for ivacaftor to be indicated.

- A number of trials have evaluated the safety and efficacy of lumacaftor/ivacaftor for the treatment of patients with CF homozygous for the *F508del* mutation.
  - Two 24-week, double-blind, placebo-controlled trials evaluated the efficacy of lumacaftor/ivacaftor in a total of 1122 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Wainwright et al 2015*). Pooled data demonstrated an improvement in ppFEV$_1$ as well as exacerbations. Based on a 96-week open-label extension study, the ppFEV$_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor; however, the improvement was not statistically significant (*Konstan et al 2017*).
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 46 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation and had severe lung disease (ppFEV$_1$ < 40) (*Taylor-Cousar et al 2018*). Dose modification to half the usual dose for 1 to 2 weeks at treatment initiation was permitted; 28 patients initiated treatment at full dose (400 mg/250 mg twice daily) and 18 patients initiated at half dose (200 mg/125 mg twice daily). The primary endpoints were safety and tolerability, which demonstrated that the most common adverse events (AEs) were respiratory in nature; patients initiating treatment at the reduced dose had less frequent respiratory events. Following an initial reduction, ppFEV$_1$ from week 4 to the end of the study was similar to baseline.
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 58 patients with CF aged 6 to 11 years who were homozygous for *F508del* (*Milla et al 2017*). At 24 weeks, there was a small improvement in ppFEV$_1$ that failed to reach statistical significance (p = 0.0671); the authors suggested that the lack of a significant effect might have been due to the small sample size and relatively mild lung disease in this population. A separate double-blind, placebo-controlled trial in 206 patients in this age group demonstrated a small but statistically significant effect on ppFEV$_1$ (*Ratjen et al 2017*).
  - An open-label, Phase 3 study evaluated the use of lumacaftor/ivacaftor in patients with CF aged 2 to 5 years who were homozygous for *F508del* (*McNamara et al 2019*). Patients weighing between 8 and 14 kg received a dose of 100 mg/125 mg and patients weighing ≥ 14 kg received a dose of 150 mg/188 mg, each given twice daily. A total of 12 patients were enrolled in part A of the study (assessing pharmacokinetics and safety over 15 days) and 60 were enrolled in part B (assessing pharmacokinetics, safety, pharmacodynamics, and efficacy over 24 weeks). The study demonstrated a reduction in mean sweat chloride concentrations, improvement in biomarkers of pancreatic function, and increased growth parameters. Safety and pharmacokinetics were consistent with previous studies of lumacaftor/ivacaftor.
- Two published Phase 3 trials have evaluated the safety and efficacy of tezacaftor/ivacaftor in patients with CF aged ≥ 12 years, and efficacy has been extrapolated to patients aged 6 to < 12 years. As with ivacaftor, tezacaftor/ivacaftor has additionally been FDA approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 24-week, double-blind trial compared tezacaftor/ivacaftor to placebo in 509 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Taylor-Cousar et al 2017*). The improvement in ppFEV$_1$ was greater with tezacaftor/ivacaftor vs placebo, and the rate of pulmonary exacerbations also favored tezacaftor/ivacaftor treatment.
  - A double-blind, crossover trial with two 8-week treatment periods evaluated tezacaftor/ivacaftor, ivacaftor monotherapy, and placebo in 246 patients with CF aged ≥ 12 years who were heterozygous for *F508del* and a second allele with a residual function mutation (*Rowe et al 2017*). Both tezacaftor/ivacaftor and ivacaftor monotherapy improved ppFEV$_1$ vs placebo, with tezacaftor/ivacaftor having a slightly larger effect than ivacaftor alone.
  - The efficacy of tezacaftor/ivacaftor in patients aged 6 to < 12 years was extrapolated from patients aged ≥ 12 years with support from population pharmacokinetic analyses showing similar tezacaftor and ivacaftor exposure levels in patients aged 6 to < 12 years to older patients. Safety of tezacaftor/ivacaftor in this population was derived from a 24-week, open-label trial in 70 patients aged 6 to < 12 years (*Symdeko prescribing information 2019*).
- Two published Phase 3 trials have evaluated the safety and efficacy of elexacaftor/tezacaftor/ivacaftor in patients with CF.
  - A 24-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor vs placebo in 403 patients ≥ 12 years of age with a single *F508del* mutation and a minimal function mutation (ie, a mutation that is nonresponsive to ivacaftor and tezacaftor/ivacaftor) (*Middleton et al 2019*). The primary endpoint, the absolute change from baseline in ppFEV$_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs placebo, with a difference of 13.8 percentage points (95% confidence interval [CI], 12.1 to 15.4; p < 0.001). Differences also favored elexacaftor/tezacaftor/ivacaftor in the change from baseline in ppFEV$_1$ through week 24, number of pulmonary

exacerbations through week 24, and changes in CFQ-R respiratory domain score, body mass index (BMI), and sweat chloride concentration.
  - A 4-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor to tezacaftor/ivacaftor in 107 patients ≥ 12 years of age who were homozygous for the *F508del* mutation (*Heijerman et al 2019*). All patients received tezacaftor/ivacaftor in a 4-week run-in period that preceded the 4-week intervention period, and baseline measurements for the intervention period reflected measurements taken after the tezacaftor/ivacaftor run-in period. The primary endpoint, the absolute change from baseline in ppFEV$_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs the tezacaftor/ivacaftor group, with a difference of 10.0 percentage points (95% CI, 7.4 to 12.6). Differences also favored elexacaftor/tezacaftor/ivacaftor in sweat chloride concentration and CFQ-R respiratory domain score.
- A systematic review and meta-analysis evaluated the use of CFTR correctors, alone or in combination with ivacaftor, vs placebo in patients with CF and class II mutations (predominantly patients homozygous for the *F508del* mutation) (*Southern et al 2018*). The authors found insufficient evidence that monotherapy with a CFTR corrector has any clinically important effects in patients homozygous for *F508del*. Lumacaftor/ivacaftor and tezacaftor/ivacaftor each resulted in similar, small improvements in clinical outcomes, including quality of life, respiratory function, and pulmonary exacerbations. With respect to tolerability, lumacaftor/ivacaftor was associated with an increase in early, transient shortness of breath and longer-term increases in blood pressure, neither of which was observed with tezacaftor/ivacaftor. The authors concluded that tezacaftor/ivacaftor has a better safety profile compared to lumacaftor/ivacaftor; however, the 2 combinations have not been directly compared.
- An additional systematic review and meta-analysis evaluated the use of CFTR modulators in patients with various genetic mutations (*Habib et al 2019*). A total of 14 trials (8 Phase 3 and 6 Phase 2) were included in the review; the elexacaftor/tezacaftor/ivacaftor triple therapy was not included.
  - The authors found that the largest improvement in ppFEV$_1$ vs placebo was demonstrated in patients with the *G551D* mutation treated with ivacaftor, with a weighted absolute mean difference of 10.8% (95% CI, 9.0 to 12.7). Patients with this mutation treated with ivacaftor also had the greatest reduction in pulmonary exacerbations.
  - Patients aged ≥ 12 years who were homozygous for the *F508del* mutation had smaller improvements vs placebo when treated with lumacaftor/ivacaftor or tezacaftor/ivacaftor. Improvements with each of these combination products were similar: 3.4% (95% CI, 2.4 to 4.4) with lumacaftor/ivacaftor and 4.0% (95% CI, 3.2 to 4.8) with tezacaftor/ivacaftor. Lumacaftor/ivacaftor and tezacaftor/ivacaftor also significantly reduced the risk of exacerbations vs placebo in patients with this genotype, but the risk reduction was less than that observed with ivacaftor in patients with the *G551D* mutation. Patients treated with lumacaftor/ivacaftor had more respiratory-related AEs leading to treatment discontinuation vs placebo.

Dornase alfa

- Pivotal trials have been conducted in CF patients with an FVC > 40% predicted and in patients with advanced lung disease (FVC < 40% predicted) (*Fuchs et al 1994, McCoy et al 1996*).
  - A 24-week, randomized, double-blind, placebo-controlled trial was conducted in 968 adults and children aged ≥ 5 years with clinically stable CF and FVC > 40% predicted (*Fuchs et al 1994*). Patients received dornase alfa 2.5 mcg once daily, dornase alfa 2.5 mcg twice daily, or placebo. A T-Updraft II Nebu-u-mist nebulizer with PulmoAide compressor was used for drug administration.
    - The administration of dornase alfa once or twice daily reduced the risk of an exacerbation requiring parenteral antibiotic treatment, although only the reduction with twice-daily dosing was statistically significant. Exacerbations requiring parenteral antibiotic therapy occurred in 27%, 22%, and 19% of patients in the placebo, once-daily, and twice-daily groups, respectively. The relative risk vs placebo was 0.78 (95% CI, 0.57 to 1.06; p = 0.11) in the once-daily dornase alfa group and 0.66 (95% CI, 0.48 to 0.91; p = 0.01) in the twice-daily group. When adjusted based on the estimated relative risk of exacerbation by patient age, the exacerbation reduction was statistically significant with both dose regimens (once daily: relative risk, 0.72; 95% CI, 0.52 to 0.98; p = 0.04; twice daily: relative risk, 0.63; 95% CI, 0.46 to 0.87; p < 0.01).
    - Dornase alfa also improved pulmonary function. FEV$_1$ improved an average of 5.8% and 5.6% with once- and twice-daily dosing, respectively, throughout the study, while placebo-treated patients did not improve (change of 0.0%) (p < 0.01 for both dose regimens vs placebo).
    - Dornase alfa also improved quality of life compared to placebo.

- A 12-week, randomized, double-blind, placebo-controlled trial was conducted in 320 patients (age range, 7 to 57 years) with clinically stable CF and FVC < 40% predicted (*McCoy et al 1996*). Patients received dornase alfa 2.5 mg once daily or placebo.
  - There were no statistically significant differences in the incidence of pulmonary exacerbations; the age-adjusted relative risk for patients treated with dornase alfa vs placebo was 0.925 (95% CI, 0.69 to 1.21; p = 0.52). However, the study may have been underpowered to detect a difference.
  - Dornase alfa significantly improved pulmonary function. The mean improvements in FEV_1 were 9.4% and 2.1% in the dornase alfa and placebo groups, respectively (p < 0.001), and the mean improvements in FVC were 12.4% and 7.3%, respectively (p < 0.01).
  - No differences were observed in dyspnea scores.
- A 2-year, randomized, double-blind, placebo-controlled trial was conducted in 474 children aged 6 to 10 years with CF and mild lung function abnormalities (FVC ≥ 85% predicted) (*Quan et al 2001*). Patients received dornase alfa 2.5 mg daily or placebo with a jet nebulizer and compressor.
  - After 2 years of therapy, patients treated with dornase alfa maintained their $ppFEV_1$ (mean change from baseline, 0.04% predicted), whereas patients treated with placebo had a decrease from baseline of 3.2% predicted (p = 0.006). Lung function benefit was also shown for the forced expiratory flow between 25% and 75% of vital capacity (difference, 7.9% predicted; p = 0.0008) and maximal expiratory flow rate at 50% of vital capacity (difference, 8.2% predicted; p = 0.0002); however, the treatment difference in FVC was not statistically significant (difference, 0.7% predicted; p = 0.51).
  - Use of dornase alfa also reduced pulmonary exacerbations. In the dornase alfa group, 40 patients (17%) had a total of 62 exacerbations, compared to 56 patients (24%) and 92 exacerbations in the placebo group (relative risk, 0.66; 95% CI, 0.44 to 1.00; p = 0.048).
- A randomized crossover study in 87 patients with CF aged ≥ 6 years compared administration of dornase alfa via a jet nebulizer to administration using the Pari eRapid electronic nebulizer (*Sawicki et al 2015*). The 2 devices led to comparable efficacy and safety, while the eRapid nebulizer was associated with shorter administration times and higher patient preference.
- A systematic review and meta-analysis evaluated the use of dornase alfa in patients with CF (*Yang and Montgomery 2018*). The review included randomized and quasi-randomized controlled trials comparing dornase alfa to placebo, standard therapy, or other medications that improve airway clearance. In all, 19 trials (N = 2565) were included, most of which compared dornase alfa to placebo. Trial duration ranged from 6 days to 3 years. Of the 19 trials included in the qualitative synthesis, 13 trials were included in the meta-analysis.
  - Compared to placebo or no dornase alfa treatment, dornase alfa was demonstrated to improve FEV_1 at various time points ranging from 1 month to 2 years. Results for efficacy at 1 month of treatment were pooled from 4 trials and demonstrated a mean improvement vs placebo of 9.51% (95% CI, 0.67 to 18.35). Results for later time points were based on a smaller number of trials and generally showed smaller improvements.
  - Pooled data for pulmonary exacerbations from 3 trials found a significant exacerbation reduction, with a risk ratio of 0.78 (95% CI, 0.62 to 0.96).
  - Effects on quality-of-life measurements such as symptoms, activity limitation, fatigue, and emotional well-being varied among trials, with some (but not all) showing significant benefits.
  - Based on 7 trials, mortality was not significantly different between dornase alfa and control groups (risk ratio, 1.7; 95% CI, 0.70 to 4.14). The majority of deaths were reported from trials in patients with severe lung disease.
  - Overall, voice alteration and rash were the only AEs associated with dornase alfa.
  - Evidence comparing dornase alfa to other medications was limited.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF). Pulmonary guidelines: use of CFTR modulator therapy in patients with CF** (*Ren et al 2018*); endorsed by the American Thoracic Society
  - This guideline provides recommendations focused on 3 main questions:
    - 1: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to gating mutations other than *G551D* or *R117H* (ie, *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*)?
    - 2: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to the *R117H* mutation?

- 3: Should lumacaftor/ivacaftor combination (vs no CFTR modulator treatment) be used in individuals with 2 copies of the *F508del* mutation?

○ A total of 30 recommendations were provided, based on the questions above and patients' age and ppFEV$_1$. These recommendations are listed in Table 3.

○ The committee chose not to address clinical situations for which recommendations have already been published (see *Mogayzel et al 2013* and *Lahiri et al 2016)* or if the question was of low priority and unlikely to change practice.

Table 3. CFF recommendations for CFTR modulators in CF treatment (2018)

Patient Age (years)	ppFEV$_1$	Certainty	Recommendation
Question 1: Ivacaftor use in patients with gating mutation other than *G551D* or *R117H*			
2 to 5	Not applicable	Not applicable	Recommended*
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Low	Conditional for
6 to 11	> 90	Low	Conditional for
12 to 17	< 40	Low	Conditional for
12 to 17	40 to 90	Moderate	Conditional for
12 to 17	> 90	Moderate	Conditional for
≥ 18	< 40	Low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Moderate	Conditional for
Question 2: Ivacaftor use in patients with *R117H* mutation			
≤ 5	Not applicable	Very low	Conditional against
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Low	Conditional against
12 to 17	< 40	Very low	Conditional for
12 to 17	40 to 90	Very low	Conditional for
12 to 17	> 90	Very low	Conditional against
≥ 18	< 40	Very low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Low	Conditional for
Question 3: Lumacaftor/ivacaftor use in patients with 2 copies of *F508del*			
≤ 5	Not applicable	Not applicable	No recommendation
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Very low	Conditional for
12 to 17	< 40	Moderate	Strong for
12 to 17	40 to 90	Moderate	Strong for
12 to 17	> 90	Low	Conditional for
≥ 18	< 40	Moderate	Strong for
≥ 18	40 to 90	Moderate	Strong for
≥ 18	> 90	Low	Conditional for

*Based on the Cystic Fibrosis Preschool Guidelines recommendations

- **CFF. CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - ○ This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. It has not been updated since 2013 and thus does not include recommendations for combination CFTR modulators; recommendations also do not reflect the expanded indications for ivacaftor.
  - ○ For these guidelines, the severity of lung disease is defined by ppFEV$_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.

- The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
- Recommendations specific to CFTR modulators and dornase alfa are shown in Table 4.

Table 4. CFF recommendations for CFTR modulators and dornase alfa in CF treatment (2013)

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Dornase alfa – moderate-to-severe disease	For individuals with CF aged ≥ 6 years with moderate-to-severe lung disease, the CFF strongly recommends the chronic use of dornase alfa to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa – mild disease	For individuals with CF aged ≥ 6 years with asymptomatic or mild lung disease, the CFF recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
2013 new or modified recommendations				
Ivacaftor	For individuals with CF aged ≥ 6 years with at least 1 *G551D CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.
B: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

- **CFF. Clinical practice guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children aged 2 to 5 years with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 5 highlights recommendations relevant to CFTR modulators and dornase alfa. The guideline does not include the more recent expanded indications for ivacaftor or recommendations for lumacaftor/ivacaftor.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force.

Table 5. CFF recommendations for CFTR modulators and dornase alfa in preschoolers aged 2 to 5 with CF (2016)

Topic	Recommendation	Grade or Consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Dornase alfa	The CFF recommends that dornase alfa be selectively offered to patients based on individual circumstances.	Moderate	Low	C
Ivacaftor	The Preschool Guidelines Committee recommends the routine use of ivacaftor in those with specific gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, and *S549R*), and a consideration for those with a confirmed diagnosis of CF and a *R117H* mutation.	Consensus Recommendation		

***C**: The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

- **Clinical Decision Support Resource: UptoDate Topic Review**
  CF: Treatment with CFTR modulators (*Simon 2019*)
  - The use of a CFTR modulator is recommended for most individuals with CF who are ≥ 12 years old and have responsive *CFTR* variants, and suggested for most younger patients with CF for whom sufficient evidence is available to allow FDA approval. Selection of a specific CFTR modulator depends on the patient's genotype and age.
  - Table 6 provides an overview of recommendations for the use of CFTR modulators. Gating and residual function mutations are listed in the boxes below the table.
    - These recommendations reflect the indications for each CFTR modulator as of October 2019 and consideration of each drug's efficacy, AEs, and potential for drug-drug interactions. Many of the recommendations were based upon comparisons of efficacy and safety data from clinical trials in which each treatment was studied independently rather than by direct comparison of multiple treatments within a single study. These recommendations are likely to change as new evidence becomes available.

Table 6. Recommendations for CFTR modulator therapy in patients with CF

Genotype	Age group	Kalydeco (ivacaftor)	Orkambi (lumacaftor/ ivacaftor)	Symdeko (tezacaftor/ ivacaftor)	Trikafta (elexacaftor/ tezacaftor/ ivacaftor)	None available
F508del homozygote	2 to 5 yrs		✔			
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
F508del heterozygote without a gating or residual function mutation	< 12 yrs					✔
	≥ 12 yrs				✔	
F508del heterozygote with gating mutation at other allele*	6 mos to 11 yrs	✔				
	≥ 12 yrs				✔	
F508del heterozygote with residual function mutation at other allele*	6 mos to 5 yrs	✔				
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
Gating mutation without *F508del*	≥ 6 mos	✔				
Residual function mutation without *F508del*	6 mos to 5 yrs	✔				
	≥ 6 yrs			✔		

Abbreviations: **mos** = months; **yrs** = years
*For patients heterozygous for *F508del* who also have gating or residual function variants, Trikafta is suggested if it is available and the patient is eligible (≥ 12 years) because the triple combination therapy is likely to be more effective than monotherapy or dual therapy.

Gating mutations approved by FDA for Kalydeco (but not Symdeko):
G1244E, G1349D, G178R, G551D, G551S, R117H, S1251N, S1255P, S549N, S549R, G1069R, R1070Q**
*Although *G1069R* and *R1070Q* are not considered prototypic gating variants, *in vitro* studies showed that ivacaftor increased their CFTR functional activity; these findings led to the FDA approval for ivacaftor.

Residual function mutations approved by FDA for Kalydeco and Symdeko:
A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G → A, 3272-26A → G, 3849+10kbC → T, 711+3A → G

SAFETY SUMMARY

- **Kalydeco (ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been reported. It is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests (LFTs) should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Kalydeco with strong cytochrome P450 (CYP) 3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor and is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Kalydeco treatment.
  - The most common adverse reactions (≥ 8% in patients with CF who have a *G551D* mutation) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.
- **Orkambi (lumacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Orkambi should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, the patients should be closely monitored and the dose should be reduced.
    - Serious adverse reactions related to elevated transaminases have been reported; in some cases associated with concomitant elevations in total serum bilirubin. ALT, AST, and bilirubin should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase or bilirubin elevations.
    - Respiratory events (eg, chest discomfort, dyspnea, and abnormal respiration) were observed more commonly in patients during initiation of Orkambi compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease ($ppFEV_1 < 40$). Clinical experience in patients with $ppFEV_1 < 40$ is limited, and additional monitoring of these patients is recommended during initiation of therapy.
    - Increased blood pressure has been observed in some patients treated with Orkambi. Blood pressure should be monitored periodically.
    - Drug interactions:
      - Lumacaftor is a strong inducer of CYP3A. Administration of Orkambi may decrease systemic exposure of CYP3A substrates. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.
      - Orkambi may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, eg, amenorrhea, dysmenorrhea, menorrhagia, and irregular menstruation (27% in women using hormonal contraceptives compared with 3% in women not using hormonal contraceptives). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.
      - Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of Orkambi with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure and is not recommended.
      - See the prescribing information for full details on drug interactions.

- Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Orkambi treatment.
- The most common adverse reactions (≥ 5% in patients with CF who are homozygous for the *F508del* mutation) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, abnormal respiration, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza.

- **Symdeko (tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Symdeko. Assessments of ALT and AST are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and may decrease exposure to tezacaftor; co-administration is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with Symdeko. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Symdeko.
  - The most common adverse reactions (≥ 3% of patients) were headache, nausea, sinus congestion, and dizziness.

- **Trikafta (elexacaftor/tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Trikafta. Bilirubin elevations have also been observed. Assessments of ALT, AST, and bilirubin are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of hepatobiliary disease or LFT elevations. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and would be expected decrease exposure to tezacaftor and elexacaftor; co-administration is not recommended.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Trikafta.
  - The most common adverse reactions (≥ 5% of patients and more frequently than with placebo by ≥ 1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increased ALT, nasal congestion, increased blood creatine phosphokinase, increased AST, rhinorrhea, rhinitis, influenza, sinusitis, and increased blood bilirubin.

- **Pulmozyme (dornase alfa):**
  - Contraindications: patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product
  - Warnings/precautions: None
  - The most common adverse reactions (≥ 3% of patients) were voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥ 10%, fever, and dyspnea.

DOSING AND ADMINISTRATION

Table 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
CFTR Modulators				
Kalydeco (ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Orkambi (lumacaftor/ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced for the first week of Orkambi treatment when co-administered with strong CYP3A inhibitors.
Symdeko (tezacaftor/ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 1 tezacaftor/ivacaftor combination tablet and the evening dose is 1 ivacaftor tablet. • Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Trikafta (elexacaftor/tezacaftor/ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 2 elexacaftor/tezacaftor/ivacaftor combination tablets and the evening dose is 1 ivacaftor tablet. • Dose should be reduced if used in patients with moderate hepatic impairment (to be used only if benefits outweigh risks). Trikafta should not be used in patients with severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
DNase Enzyme				
Pulmozyme (dornase alfa)	Inhalation solution	Inhalation (with nebulizer)	Once daily; some patients may benefit from twice-daily administration	• Administered using a recommended jet nebulizer/compressor system or eRapid Nebulizer System.

See the current prescribing information for full details.

CONCLUSION

- The CFTR modulators, Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor), are used in the long-term management of CF in patients eligible for such treatment based on their age and specific *CFTR* mutations. These products act to facilitate processing and trafficking of CFTR to the cell surface or to increase chloride transport at the cell surface. These products have been demonstrated to improve lung function; some trials also demonstrated improvement in reducing pulmonary exacerbations and/or improving quality of life.
  - The approval of Trikafta expanded the population of patients eligible for highly effective CFTR modulator therapy. As a result of the Trikafta approval and expanded indications for existing agents, the majority of patients with CF have become eligible for CFTR modulator therapy.
  - Key warnings/precautions with the CFTR modulators include the risk of elevated transaminases, cataracts, and drug interactions. A key additional warning for Orkambi is the risk of respiratory events (eg, chest discomfort, dyspnea, and

abnormal respiration). Orkambi has also been associated with worsening of liver function in patients with advanced liver disease, and has more significant drug interactions than the other CFTR modulators.
  - The CFTR modulators are dosed orally twice daily.
- Pulmozyme (dornase alfa) is another key treatment used in the long-term management of CF. It works to reduce sputum viscoelasticity. Guidelines recommend its use in patients aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations).
  - Pulmozyme has no warnings/precautions listed in its prescribing information.
  - Pulmozyme is administered by inhalation with a nebulizer. Recommended dosing is once daily, although some patients may benefit from twice-daily administration.

APPENDICES

Appendix A: Additional Information on CFTR Modulators

Table 8. Overview of Key Clinical Trials for CFTR Modulators

Trial/Reference	Design/Population	Key Results	Comments/ Additional Data
Kalydeco (ivacaftor)			
STRIVE *Ramsey et al 2011*	Phase 3, 48-week, DB, PC trial in 167 patients aged ≥ 12 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 10.4 percentage points from baseline; difference from placebo, 10.6 percentage points (95% CI, 8.6 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, and sweat chloride. Improvements were maintained through week 48.
ENVISION *Davies et al 2013*	Phase 3, 48-week, DB, PC trial in 52 patients aged 6 to 11 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 12.6 percentage points from baseline; difference from placebo, 12.5 percentage points (95% CI, 6.6 to 18.3; p < 0.0001)	Secondary endpoints: Improvements were observed in weight and sweat chloride. The improvement in CFQ-R (child version) did not reach statistical significance (TD, 6.0 points; p = 0.109); however, the parent/caregiver version did (TD, 5.9 points; p = 0.033). No statistically significant difference in exacerbations was demonstrated.
PERSIST *McKone et al 2014*	Phase 3, 96-week, OLE study of STRIVE and ENVISION; enrolled 192 patients aged ≥ 6 yrs with ≥ 1 *G551D* mutation; all received ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate and resolved during the reporting period; safety was consistent with the PC period of the trial $ppFEV_1$ (secondary endpoint): Improvements in FEV_1 were sustained through the 96-week extension period	Additional secondary endpoints: Improvements were sustained for weight gain, CFQ-R, and exacerbation rate.

KONNECTION *De Boeck et al 2014*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 39 patients aged ≥ 6 yrs with non-*G551D* gating mutation	$ppFEV_1$: 8 weeks: 7.5 percentage points from baseline; difference from placebo, 10.7 percentage points (95% CI, 7.3 to 14.1; p < 0.0001)	Secondary endpoints: Improvements were observed in weight, sweat chloride, and CFQ-R.
KONDUCT *Moss et al 2015*	Phase 3, 24-week, DB, PC trial in 69 patients aged ≥ 6 yrs with *R117H* mutation	$ppFEV_1$: 24 weeks: 2.6 percentage points from baseline; difference from placebo, 2.1 percentage points (95% CI, -1.13 to 5.35; p = 0.20); in a pre-specified subgroup analysis, $ppFEV_1$ significantly improved with ivacaftor in patients aged ≥ 18 yrs, with a TD vs placebo of 5.0 percentage points (95% CI, 1.15 to 8.78), but not in patients aged 6 to 11 yrs, with a TD vs placebo of -6.3 percentage points (95% CI, -11.96 to -0.71; p = 0.03)	Secondary endpoints: Improvements were observed in sweat chloride and CFQ-R. The lack of effect for $ppFEV_1$ in the pediatric and overall populations may be related in part to the fact that pediatric patients had a high baseline $ppFEV_1$. Most patients (N = 65) entered a washout period followed by an OLE period; at a 12-week analysis, patients in both the placebo-to-ivacaftor and ivacaftor-to-ivacaftor groups showed a significant $ppFEV_1$ improvement from post-washout baseline (5.0 [p = 0.0005] and 6.0 [p = 0.0006] percentage points, respectively).
EXPAND *Rowe et al 2017* *(ivacaftor and placebo arms)*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation (of these, 157 and 162 patients were treated with ivacaftor and placebo, respectively)	$ppFEV_1$: Average of 4 and 8 week assessments: difference from placebo, 4.7 percentage points (95% CI, 3.7 to 5.8; p < 0.001)	Secondary endpoint: Improvements were observed for ivacaftor vs placebo for CFQ-R. Benefits were also observed for other secondary endpoints, but statistical significance cannot be claimed due to the statistical design.
KIWI *Davies et al 2016*	Phase 3, 24-week, OL study in 34 patients aged 2 to 5 yrs with ≥ 1 *CFTR* gating mutation; patients received a dose of 50 mg (weight 8 to 14 kg) or 75 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposure was similar to that reported with the approved dosing in adults Safety: Safety was similar to use in adults, although there was an increased incidence of LFT elevations; most AEs were mild or moderate; common AEs included cough and vomiting	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. No meaningful data on lung function were available (spirometry results are limited in this age group).

ARRIVAL *Rosenfeld et al 2018*	Phase 3, 24-week, OL study in 19 patients aged 12 to < 24 months with a *CFTR* gating mutation on ≥ 1 allele (study part B); patients received a dose of 50 mg (weight 7 to 14 kg) or 75 mg (weight ≥ 14 to < 25 kg), each given twice daily	Pharmacokinetics: Exposure of ivacaftor was similar to that in older children in adults The safety profile was consistent with experience in older children; most AEs were mild or moderate and considered unlikely to be (nor not) related to ivacaftor; 27.8% of patients had elevated ALT and/or AST > 3 x ULN	Secondary endpoint: Improvements were demonstrated in sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Mean serum lipase and amylase were elevated at baseline and decreased rapidly with ivacaftor. Growth status was generally well maintained.
Orkambi (lumacaftor/ivacaftor)			
TRAFFIC and **TRANSPORT** *Wainwright et al 2015*	Two Phase 3, 24-week, DB, PC trials in 1122 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks, pooled data: 2.5 percentage points from baseline; difference from placebo, 2.8 percentage points (95% CI, 1.8 to 3.8; p < 0.001)	Secondary endpoints: In the pooled analysis, there were improvements in weight and exacerbations. The difference in CFQ-R did not reach statistical significance, with an improvement of 2.2 (95% CI, 0.0 to 4.5; p = 0.05).
PROGRESS *Konstan et al 2017*	Phase 3, 96-week, OLE study of TRAFFIC and TRANSPORT; enrolled 1030 patients aged ≥ 12 yrs homozygous for *F508del*; all received lumacaftor/ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate; rates of AEs were similar or reduced to rates during the PC period of the trial; an increase in blood pressure was noted $ppFEV_1$ (secondary endpoint): Mean $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor, but the improvement was not statistically significant	Additional secondary endpoints: The pulmonary exacerbation rate remained low. Improvements in BMI and CFQ-R continued throughout the study. Analysis of lung function change over time showed a slower rate of decline compared to matched registry patients.
Taylor-Cousar et al 2018	Phase 3b, 24-week, OL study in 46 patients aged ≥12 yrs homozygous for *F508del* who had advanced lung disease ($ppFEV_1$ < 40); 28 received lumacaftor/ ivacaftor at the usual dose (400 mg/250 mg twice daily) and 18 patients initiated at half-dose (200 mg/125 mg twice daily) for	Safety/tolerability: The most common AEs were respiratory in nature (infective pulmonary exacerbation, abnormal respiration, cough, dyspnea); patients initiating on half-dose had less frequent respiratory events (56% vs 71%) and events were of shorter duration (median 4 vs 9	Secondary endpoints: There was an initial decrease in $ppFEV_1$ that returned to baseline at week 4 and remained near baseline throughout the remainder of the study. Improvements vs baseline were seen in sweat chloride and BMI. Reductions in intravenous antibiotics and all-cause hospitalization were shown between the study period and the 24-week period prior to the study. Improvements in CFQ-R were not

	1 to 2 weeks before increasing to full-dose	days); 5 patients (11%) had ALT or AST elevation > 3 x ULN	statistically significant.
Milla et al 2017	Phase 3, 24-week, OL study in 58 patients aged 6 to 11 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 2.5 percentage points from baseline (95% CI, -0.2 to 5.2; p = 0.0671)	Secondary endpoints: Improvements from baseline were seen in sweat chloride, weight, and CFQ-R. The small sample size and relatively mild lung disease in this population may explain the lack of significant effect on $ppFEV_1$. The safety profile was similar to that seen in larger trials in older patients.
Ratjen et al 2017	Phase 3, 24-week, DB, PC trial in 206 patients aged 6 to 11 yrs homozygous for *F508del*	Mean change in lung clearance index ($LCI_{2.5}$; see Appendix B) from baseline to average of all visits up to and including week 24 (primary endpoint): -1.0 with lumacaftor/ivacaftor vs 0.1 with placebo; TD, -1.1 (95% CI, -1.4 to -0.8; p < 0.0001) $ppFEV_1$: Average of all visits up to and including week 24: 1.1 percentage points from baseline; difference from placebo, 2.4 percentage points (95% CI, 0.4 to 4.4; p = 0.0182)	Additional secondary endpoints: Improvements were observed in sweat chloride. Changes in BMI and CFQ-R were not statistically significant.
McNamara et al 2019	Phase 3, 24-week, OL study in 60 patients aged 2 to 5 yrs homozygous for *F508del* (study part B); patients received a dose of 100 mg/125 mg (weight 8 to 14 kg) or 150 mg/188 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposures of both lumacaftor and ivacaftor were within the targeted range for older patients and similar to concentrations previously reported The safety profile was consistent with experience in adults; 10% of patients had respiratory AEs (dyspnea, abnormal respiration, wheezing); 15% had increased ALT and/or AST > 3 x ULN	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Limited data on lung function were available (spirometry results are limited in this age group). $LCI_{2.5}$ demonstrated a numerical, nonsignificant improvement (exploratory/optional endpoint).

Symdeko (tezacaftor/ivacaftor)			
EVOLVE *Taylor-Cousar et al 2017)*	Phase 3, 24-week, DB, PC trial in 509 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 3.4 percentage points from baseline; difference from placebo, 4.0 percentage points (95% CI, 3.1 to 4.8; p < 0.001)	Secondary endpoints: Patients treated with tezacaftor/ivacaftor had a reduced number of pulmonary exacerbations. Numerical improvements were seen in BMI, CFR-Q, and sweat chloride. The change in BMI was not statistically significant, and the changes in CFQ-R and sweat chloride were not assessed for statistical significance due to the testing hierarchy. The rate of respiratory AEs was not higher in the tezacaftor/ivacaftor group than the placebo group; this compares favorably to studies with lumacaftor/ivacaftor.
EXPAND *Rowe et al 2017*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation	$ppFEV_1$: 8 weeks: difference for tezacaftor/ivacaftor vs placebo, 6.8 percentage points (95% CI, 5.7 to 7.8; p < 0.0001); difference for tezacaftor/ivacaftor vs ivacaftor, 2.1 percentage points (95% CI, 1.2 to 2.9; p < 0.0001)	Secondary endpoints: Improvement was seen in CFQ-R for tezacaftor/ivacaftor vs placebo; the difference in CFQ-R between tezacaftor/ivacaftor and ivacaftor was not statistically significant. A numerical improvement was observed in sweat chloride, but significance was not assessed due to the statistical hierarchy.
Trikafta (elexacaftor/tezacaftor/ivacaftor)			
VX17-445-102 *Middleton et al 2019*	Phase 3, 24-week, DB, PC trial in 403 patients aged ≥ 12 years heterozygous for *F508del* and a minimal function mutation	$ppFEV_1$: 4 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 13.8 percentage points (95% CI, 12.1 to 15.4; p < 0.001) 24 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 14.3 percentage points (95% CI, 12.7 to 15.8; p < 0.001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, sweat chloride, and BMI.

VX17-445-103 *Heijerman et al 2019*	Phase 3, 4-week, DB, AC trial in 107 patients aged ≥ 12 years homozygous for *F508del*	ppFEV$_1$: 4 weeks: difference for elexacaftor/tezacaftor/ivacaftor vs tezacaftor/ivacaftor: 10.0 percentage points (95% CI, 7.4 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were seen in CFQ-R score and sweat chloride. Exacerbations were not defined as an efficacy endpoint, but were reported as an AE less frequently in the elexacaftor/tezacaftor/ivacaftor group than in the tezacaftor/ivacaftor group. BMI was not defined as an efficacy endpoint but increased more in the elexacaftor/tezacaftor/ivacaftor group (nominal p < 0.0001).

Note: CFQ-R scores refer to the respiratory domain.
Abbreviations: **AC** = active-controlled, **AE** = adverse event, **ALT** = alanine aminotransferase, **AST** = aspartate aminotransferase, **BMI** = body mass index, **CFQ-R** = cystic fibrosis questionnaire-revised, **CI** = confidence interval, **DB** = double-blind, **LCI** = lung clearance index, **LFT** = liver function test, **OL** = open-label, **OLE** = open-label extension, **PC** = placebo-controlled, **ppFEV$_1$** = percent predicted forced expiratory volume in 1 second, **TD** = treatment difference, **ULN** = upper limit of normal, **XO** = crossover, **yrs** = years

Appendix B: Study endpoint descriptions

- **CF Questionnaire (CFQ); CF Questionnaire-Revised (CFQ-R)** (*American Thoracic Society 2002, Quittner et al 2009*)
  - This is a disease-specific quality-of-life instrument designed to measure impact of CF on overall health, daily life, perceived well-being, and symptoms.
  - The CFQ-R has 9 quality-of-life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, and health perceptions) and 3 symptom scales (weight, respiratory, and digestion).
  - Scaling of items uses 4-point Likert scales (eg, always/often/sometimes/never).
  - Each health-related quality-of-life domain is scored. Standardized scores range from 0 to 100, with higher scores indicating better quality of life.
  - The minimal clinically important difference in CFQ-R respiratory scores has been estimated to be approximately 8.5 points in patients experiencing a CF exacerbation and 4.0 points in stable CF patients.
- **Lung Clearance Index (LCI$_{2.5}$)** (*Ratjen et al 2017*)
  - This is a measure of the number of lung volume turnovers required to reach 2.5% of tracer gas concentration.
  - Elevated LCI$_{2.5}$ values reflect increasing unevenness of gas mixing within the lung caused by early lung disease secondary to mucus plugging and airway wall changes.
  - LCI$_{2.5}$ may be more sensitive than FEV$_1$ for the presence of early structural lung abnormalities, particularly in the pediatric population.
- **Sweat chloride test** (*Durmowicz et al 2013, Farrell et al 2017*)
  - This test measures the amount of chloride in a patient's sweat. It is considered the gold standard for diagnosis of CF.
  - A sweat test concentration of ≥ 60 mmol/L indicates a diagnosis of CF, and a concentration of < 30 mmol/L indicates that CF is unlikely. Patients with results in the intermediate range (30 to 59 mmol/L) and certain clinical characteristics (positive newborn screen, symptoms of CF, or a positive family history) may have CF and further testing should be considered.
  - Based on the diagnostic relationship between sweat chloride and CF, change in sweat chloride has been used as a measure of CFTR function and as a pharmacodynamic endpoint in clinical trials. A reduction in sweat chloride has been demonstrated in clinical trials of CFTR modulators. However, a correlation between changes in sweat chloride and improvements in FEV$_1$ has not been consistently demonstrated, and there is no specific improvement in sweat chloride concentration that can predict FEV$_1$ improvement. This may be related to the multiple physiologic, environmental, and genetic factors that modulate CF severity.

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Publication Date: January 16, 2020

Prior Authorization Guideline

Guideline Name	Narcolepsy Agents

1 . Indications

Drug Name: Wakix (pitolisant)
Narcolepsy Indicated for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy.

2 . Criteria

Product Name: Wakix	
Diagnosis	Narcolepsy
Approval Length	6 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of narcolepsy as confirmed by sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible) [A, B]

Product Name: Wakix	
Diagnosis	Narcolepsy

Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Wakix therapy

3 . Endnotes

A. International Classification of Sleep Disorders (ICSD-3) diagnostic criteria for narcolepsy type 1 (narcolepsy with cataplexy) require: 1) Daily periods of irrepressible need to sleep or daytime lapses into sleep (i.e., excessive daytime sleepiness) occurring for at least 3 months. 2) The presence of one or both of the following: cataplexy and a mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT; or cerebrospinal fluid (CSF) hypocretin-1 concentration is low (less than or equal to 110 pg/mL or less than one-third of mean values obtained in normal subjects with the same standardized assay) [2,3].

B. International Classification of Sleep Disorders (ICSD-3) diagnostic criteria for narcolepsy type 2 (narcolepsy without cataplexy) include: 1) Daily periods of irrepressible need to sleep or daytime lapses into sleep (i.e., excessive daytime sleepiness) occurring for at least 3 months. 2) Cataplexy is absent. 3) CSF hypocretin-1 levels, if measured, is either greater than 100 pg/mL or greater than one-third of mean values obtained in normal subjects with the same standardized assay. 4) A mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT. 5) Hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal [2,3].

4 . References

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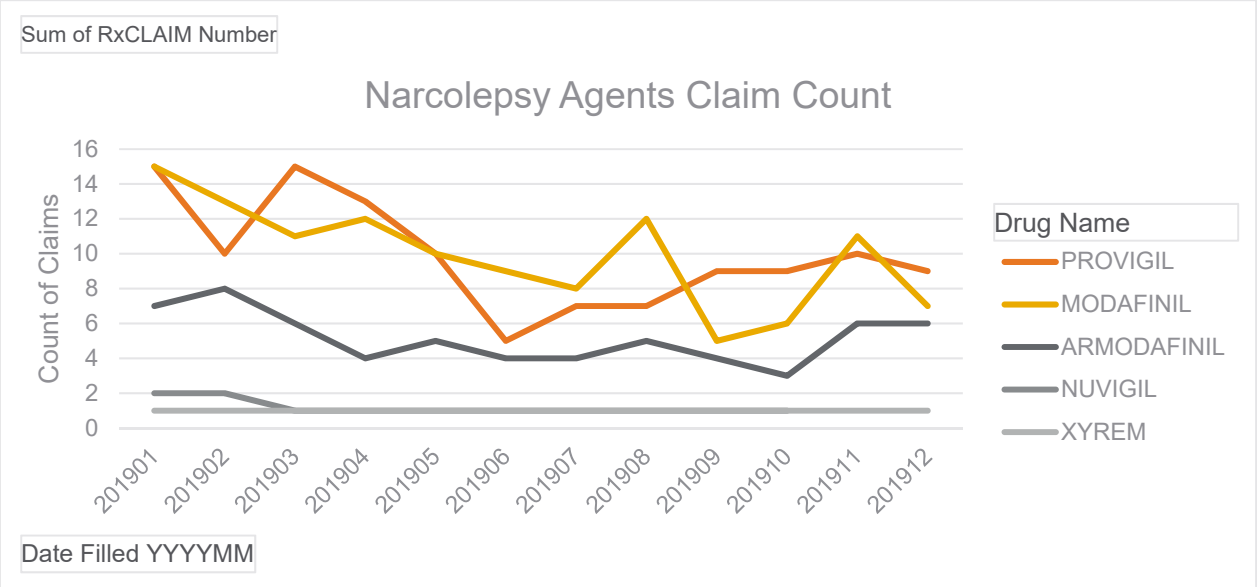
Nevada Medicaid

Narcolepsy Agents
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
PROVIGIL	25	119	2,650	2,713
ARMODAFINIL	12	62	1,861	1,861
MODAFINIL	29	119	3,230	3,874
NUVIGIL	1	13	340	680
XYREM	1	12	360	6,300



AAA. Xyrem® (sodium oxybate), Provigil® (modafinil), Nuvigil® (armodafinil)

Therapeutic Class: Narcolepsy Agents (non-stimulants)
Last Reviewed by the DUR Board: April 23, 2015

Xyrem® (sodium oxybate), Provigil® (modafinil), Nuvigil® (armodafinil) are subject to prior authorizations and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. Provigil® (modafinil), and Nuvigil® (armodafinil):

      1. The recipient has a diagnosis of narcolepsy.

   b. Xyrem® (sodium oxybate):

      1. The recipient has tried and failed on Provigil® (modafinil) or Nuvigil® (armodafinil); and/or

      2. The recipient has a diagnosis of narcolepsy with cataplexy; and

      3. The drug was prescribed by or in consultation with a neurologist or sleep specialist.

2. Prior Authorization Guidelines

   a. Prior authorization approvals will be for one year.

   b. Prior Authorization forms are available at:
   http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Narcolepsy Agents

INTRODUCTION

- Narcolepsy is a lifelong neurological sleep disorder of hypersomnia characterized by excessive daytime sleepiness (EDS) and intermittent manifestations of rapid eye movement (REM) sleep during wakefulness. Excessive sleepiness is defined by the International Classification of Sleep Disorders, third edition (ICSD-3) as "daily episodes of an irrepressible need to sleep or daytime lapses into sleep" (*Sateia 2014*).
- Patients with narcolepsy often have many nighttime arousals and sleep disturbances that contribute to excessive drowsiness during the day. EDS can vary in severity, and some patients involuntarily fall asleep during normal daily activities. This can put the patient or others at risk if these daytime lapses into sleep occur during activities such as operating a motor vehicle. While all patients with narcolepsy experience EDS, additional symptoms may include cataplexy, which is the sudden and complete loss of muscle tone, dream-like images or hallucinations at sleep onset or awakening, and sleep paralysis (*National Institute of Neurological Disorders and Stroke [NINDS] 2017, Scammell 2019).*
- The ICSD-3 establishes 2 subtypes of narcolepsy: narcolepsy type 1 and narcolepsy type 2. Patients are diagnosed with narcolepsy type 1 if they have 1 or both of the following: (1) a cerebrospinal fluid (CSF) hypocretin-1 deficiency; (2) clear cataplexy and a mean sleep latency of < 8 minutes on the multiple sleep latency test (MSLT) with evidence of 2 sleep-onset rapid-eye movement periods (SOREMPs), one of which may be seen on a preceding overnight polysomnogram. A diagnosis of narcolepsy type 2 also requires a mean sleep latency of < 8 minutes on the MSLT and at least 2 SOREMPs, but cataplexy must be absent and CSF hypocretin-1 levels must not meet the type 1 criterion *(Sateia 2014).*
- Narcolepsy affects males and females equally. While symptoms typically begin to present in the teens or early twenties, they can occur at any time throughout a patients' life (*NINDS 2017, Scammell 2019*). It is estimated that approximately 135,000 to 200,000 people in the United States (US) are diagnosed with narcolepsy; however, this number may actually be higher as many patients often go undiagnosed (*NINDS 2017).* Narcolepsy is a chronic condition, but does not typically get worse over time. There is no cure for narcolepsy, but there are pharmacological and nonpharmacological options that can be implemented to help patients manage their symptoms. The goal of therapy is to mitigate symptoms in order to improve the patient's quality of life (*Morgenthaler et al 2007a, NINDS 2017*).
- This review will focus on 2 wakefulness promoting agents, modafinil (Provigil) and armodafinil (Nuvigil), 1 central nervous system (CNS) depressant agent, sodium oxybate (Xyrem), 1 dopamine norepinephrine reuptake inhibitor (DNRI), solriamfetol (Sunosi), and 1 histamine H_3 antagonist/inverse agonist, pitolisant (Wakix). These 5 medications are approved by the US Food and Drug Administration (FDA) for the symptomatic treatment of narcolepsy. There are several amphetamine-like stimulant medications indicated for the treatment of narcolepsy; however, they will not be covered in this review.
- Modafinil and armodafinil (the longer half-life R-enantiomer of modafinil) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), and shift work disorder (SWD). OSA is a sleep disorder that is characterized by obstructive apneas and hypopneas, causing patients to have frequent sleep interruptions due to increased respiratory effort. Often, patients do not feel rested in the morning and continue to have excessive sleepiness throughout the day (*American Academy of Sleep Medicine [AASM] 2009*). SWD is a circadian rhythm sleep disorder that occurs in individuals who work non-traditional hours and is characterized by excessive sleepiness and/or insomnia (*Morgenthaler et al 2007b*). Modafinil and armodafinil have been shown to produce psychoactive and euphoric effects similar to CNS stimulants, as well as alterations in mood, perception, thinking and feelings. As a result, these agents are classified as Schedule IV controlled substances.
- Pitolisant is an H_3 antagonist/inverse agonist. Although it has been studied in patients with narcolepsy with cataplexy, it is currently only approved for the treatment of narcolepsy. Pitolisant has shown no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy (*FDA web site*).
- Sodium oxybate is gamma-hydroxybutyric acid (GHB), a known drug of abuse. It is FDA-approved for the treatment of EDS and cataplexy in patients ≥ 7 years of age with narcolepsy and is classified as a Schedule III controlled substance for these indications. However, non-medical uses of sodium oxybate are classified under Schedule I. Sodium oxybate carries a boxed warning regarding CNS depression, abuse, and misuse, and may only be dispensed to patients enrolled

in the Xyrem Risk Evaluation and Mitigation Strategy (REMS) program using a specially certified pharmacy. Prescribers and patients must also be enrolled in this REMS program (*Xyrem REMS Web site).*

- Solriamfetol is FDA-approved to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA. Solriamfetol is a Schedule IV controlled substance (*Sunosi dossier 2019*).
- While placebo-controlled (PC) clinical studies document the efficacy of these agents, the exact mechanisms of action are not completely understood. Head-to-head studies are limited, and current clinical guidelines recommend modafinil and sodium oxybate as first-line treatments for EDS and cataplexy, respectively.
- Medispan class: See Table 1 below

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants - Misc	
Nuvigil (armodafinil)	✔
Provigil (modafinil)	✔
Dopamine and Norepinephrine Reuptake Inhibitors (DNRIs)	
Sunosi (solriamfetol)	-
Histamine H_3-Receptor Antagonist/Inverse Agonists	
Wakix (pitolisant)	-
Anti-Cataplectic Agents	
Xyrem (sodium oxybate)	-

(*Drugs@FDA 2020, Orange Book: approved drug products with therapeutic equivalence evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Nuvigil (armodafinil)	Provigil (modafinil)	Sunosi (solriamfetol)	Wakix (pitolisant)	Xyrem (sodium oxybate)
Improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD	✔	✔			
Treatment of EDS in adult patients with narcolepsy				✔	
Improve wakefulness in adult patients with EDS associated with narcolepsy or OSA			✔		
Treatment of cataplexy and EDS in narcolepsy in patients ≥ 7 years of age					✔

(*Prescribing information: Nuvigil 2019, Provigil 2019, Sunosi 2019, Wakix 2019, Xyrem 2018*)

- 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

Narcolepsy

- The efficacy of modafinil for EDS associated with narcolepsy was established in 2 multicenter (MC), double-blind (DB), PC, randomized controlled trials (RCTs). In both studies, patients treated with modafinil showed statistically significant improvement in objective measures of excessive sleepiness as measured by the MSLT and Maintenance of Wakefulness Test (MWT); and the subjective Epworth Sleepiness Scale (ESS) compared to placebo ($p < 0.001$ for all endpoints in both studies). Overall clinical condition as rated by the Clinical Global Impression of Change (CGI-C) at the final visit was also significantly improved over baseline for patients treated with modafinil compared to placebo in both

studies (p < 0.005 and p < 0.03) (*US Modafinil in Narcolepsy Multicenter Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000).*

- The efficacy of armodafinil for EDS associated with narcolepsy was established in a MC, DB, PC, RCT. Patients treated with armodafinil showed a statistically significant enhanced ability to remain awake as measured by the MWT compared to placebo (p < 0.01), as well as improvement in overall clinical condition as rated by the CGI-C compared to placebo (p < 0.0001). Armodafinil was also associated with statistically significant improvements in memory, attention, and fatigue (p < 0.05) (*Harsh et al 2006).*
- The efficacy and safety of pitolisant were evaluated in two 8-week, Phase 3, active-controlled, DB, PC, MC, RCTs evaluating the treatment of EDS in adults with narcolepsy with or without cataplexy (HARMONY 1 and HARMONY 1bis) (*Dauvilliers et al 2013*, *Wakix dossier 2019, Wakix FDA clinical review 2019*).
  - HARMONY 1 (N = 95) compared pitolisant 10, 20, or 40 mg per day to modafinil 100, 200, or 400 mg per day. Of the 94 patients in the intent-to-treat (ITT) analysis, 81% had cataplexy, 45% had received psychostimulants (mostly modafinil or methylphenidate) and 35% were receiving anticataplectic drugs and continued them at stable doses during the trial (sodium oxybate, n = 8; antidepressants, n = 25). The primary analysis of between-group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (p = 0.024), but not non-inferior to modafinil (p = 0.250).
    - A post-hoc analysis of ESS responder rate (final ESS score ≤ 10) showed a significantly greater response with pitolisant vs placebo (p < 0.0006) and a similar response between pitolisant and modafinil (p = 0.908).
    - MWT values decreased from baseline in the placebo group but improved in the pitolisant group demonstrating superiority of pitolisant (p = 0.044). MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (p = 0.173).
  - HARMONY 1bis (*Wakix dossier 2019, Wakix FDA clinical review 2019*) compared pitolisant titrated to 20 mg per day to modafinil 200 to 400 mg/day in 166 patients. Of the 164 patients included in the extended ITT population, a history of cataplexy was present in 75% of patients in the pitolisant group, 77% in the modafinil group, and 81% in the placebo group.
    - The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority (p = 0.036). The non-inferiority of pitolisant compared to modafinil could not be concluded (p = 0.002), most likely due to an imbalance between dosages of both drugs and the short treatment period.
    - The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (p = 0.002). There was no significant difference between pitolisant and modafinil (p = 0.052).
    - MWT values decreased from baseline in the placebo group but improved in the pitolisant group (p = 0.022). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and modafinil was seen (p = 0.198).
- A 12-month, open-label (OL), MC, uncontrolled longitudinal study (HARMONY III) was conducted to evaluate the long-term safety of pitolisant (*Dauvilliers et al 2019*). Patients (N = 102, 75 with cataplexy) received pitolisant of whom 73 were treatment-naïve. Sixty-eight patients (51 with cataplexy) completed the 12-month treatment. Common treatment-emergent adverse events (AEs) were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depressive symptoms (4.9%), and nausea (4.9%). Seven patients had a serious AE, unrelated to pitolisant except for a possibly related miscarriage. One-third of patients stopped pitolisant, mostly (19.6%) for insufficient efficacy. ESS score decreased by 4.6 ± 0.6. Two-thirds of patients completing the treatment were responders (ESS ≤ 10 or ESS decrease ≥ 3), and one-third had normalized ESS (≤ 10). Complete and partial cataplexy, hallucinations, sleep paralysis, and sleep attacks were reduced by 76%, 65%, 54%, 63%, and 27%, respectively.
- The effectiveness of sodium oxybate in the treatment of EDS in patients with narcolepsy was established in 2 MC, DB, PC, RCTs.
  - In the first study, patients treated with sodium oxybate 6 and 9 grams per night achieved statistically significant improvements on the ESS, MWT, and CGI-C compared to the placebo group (p < 0.001 for all) (*Xyrem International Study Group 2005a*).
  - The second study required patients to be taking a stable dose of modafinil before study randomization. Patients were randomized to placebo, sodium oxybate, modafinil, or sodium oxybate plus modafinil. Patients who were switched from modafinil to sodium oxybate did not experience any decrease in sleep latency, suggesting that both medications are equally effective for EDS. Patients taking sodium oxybate alone and sodium oxybate plus modafinil had statistically significant improvements in sleep latency from baseline as measured by MWT compared to the placebo

group ($p < 0.001$). The sodium oxybate plus modafinil group showed a significantly greater increase in sleep latency from baseline compared to the sodium oxybate alone group ($p < 0.001$), suggesting that the combination of drugs had an additive effect (*Black & Houghton 2006*).

- The efficacy of sodium oxybate in the treatment of cataplexy in patients with narcolepsy was established in 2 DB, PC, RCTs.
  - In the first study, patients treated with 6 and 9 grams per night saw a significant decrease in cataplexy attacks compared to placebo ($p < 0.05$ for both doses) (*U.S. Xyrem Multicenter Study Group 2002*).
  - The second study was a randomized withdrawal trial including narcoleptic patients already established on sodium oxybate therapy prior to study entry. Patients were randomized to continue treatment with sodium oxybate or to placebo, which included discontinuation of sodium oxybate therapy. Patients who discontinued sodium oxybate experienced a significant increase in cataplexy attacks compared to patients who remained on sodium oxybate ($p < 0.001$) (*U.S. Xyrem Multicenter Study Group 2004*).
- The efficacy of solriamfetol for the treatment of narcolepsy or narcolepsy with cataplexy was evaluated in a DB, PC, MC, RCT (*Thorpy et al 2019*). Patients were stratified on the basis of presence or absence of cataplexy. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups. At week 12, treatment with solriamfetol significantly improved mean sleep latency measured by the MWT vs placebo ($p < 0.0001$) and ESS scores ($p \leq 0.02$). Significantly higher percentages of patients treated with solriamfetol also reported improvements in Patient Global Impression of Change (PGI-C) vs placebo ($p < 0.0001$). There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).
- Although not FDA-approved for treatment of narcolepsy with cataplexy, pitolisant has demonstrated efficacy in 1 DB, PC, MC, RCT in 106 patients *(*HARMONY CTP; *Szakacs et al 2017*). From a baseline weekly cataplexy rate (WCR) of 9.15 in the pitolisant group and 7.31 in the placebo group, the WCR was significantly reduced by a relative 75% in the pitolisant group compared with 38% in the placebo group ($p < 0.0001$). For almost all secondary endpoints, a significant superiority of pitolisant was shown (ie, proportion of patients with WCR > 15 at the end of treatment, mean ESS decrease, patient proportion with final ESS ≤ 10, MWT mean change, CGI-C, Patient's global opinion (PGO), and frequency of hallucinations).

OSA

- The efficacy of modafinil for EDS associated with OSA was established in 2 DB, PC, RCTs. In both studies, patients treated with modafinil saw a statistically significant improvement in wakefulness compared to placebo ($p < 0.001$ for both) (*Black et al 2005, Pack et al 2001*).
- The efficacy of armodafinil for EDS associated with OSA was established in 2 PC, DB, RCTs. In both studies, patients treated with armodafinil showed a statistically significant improvement in the ability to remain awake as measured by the MWT ($p < 0.001$ and $p = 0.0003$) and overall clinical condition per the CGI-C compared to placebo ($p < 0.001$ and $p = 0.0069$) (*Roth et al 2006, Hirshkowitz et al 2007*).
- The efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment was demonstrated in a DB, PC, MC, RCT (*Schweitzer et al 2018*). At week 12, solriamfetol-treated patients had significantly greater improvements in mean sleep latency assessed by the MWT ($p < 0.001$) and ESS score ($p \leq 0.02$). At week 12, higher percentages of patients on solriamfetol reported overall improvement on the PGI-C vs placebo ($p < 0.0001$).
- A randomized withdrawal study evaluated the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA (*Strollo et al 2019*). After 2 weeks of clinical titration and 2 weeks of stable dose administration, patients who reported "much improved" or "very much improved" on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks. From baseline to week 4, mean sleep latency on the MWT and ESS scores improved. From weeks 4 to 6 (randomized withdrawal phase), solriamfetol-treated patients maintained improvements in MWT and ESS. During the randomized withdrawal phase, more patients who were switched to placebo reported worsening on the PGI-C and CGI-C vs those who continued solriamfetol.
- An OL extension study evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Sunosi dossier 2019*). In a 2-week OL titration phase, patients received solriamfetol, titrated to a maximum tolerated dose, followed by a maintenance phase. During a 2-week PC randomized withdrawal phase ~6 months later, patients were randomized

either to placebo or to continue their maintenance solriamfetol dose for 2 weeks. From the beginning to the end of the randomized withdrawal phase, the ESS score was significantly improved with solriamfetol vs placebo ($p < 0.0001$). The percentage of patients who were reported as worse on the PGI-C at the end of the randomized withdrawal phase was greater for patients randomized to placebo compared to patients on solriamfetol ($p < 0.0001$). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores. During the randomized withdrawal period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

SWD

- The efficacy of modafinil in treating EDS associated with SWD was evaluated in a DB, PC, RCT. Patients treated with modafinil showed a statistically significant improvement in nighttime sleep latency as measured by the MSLT ($p = 0.002$) (*Czeisler et al 2005*).
- The efficacy of armodafinil in treating EDS associated with SWD was evaluated in a DB, PC, RCT. Patients treated with armodafinil showed a statistically significant improvement in sleep latency as measured by nighttime MSLT compared to placebo ($p < 0.001$) (*Czeisler et al 2009*).
- A head-to-head study conducted by Tembe et al compared armodafinil to modafinil in patients with SWD. The study compared the response rate, defined as the proportion of patients showing ≥ 2 grades of improvement based on the Stanford Sleepiness Score (SSS). After 12 weeks of therapy, there was no statistically significant different in response rates between patients treated with armodafinil vs modafinil ($p = 0.76$). Compliance to therapy and adverse events (AEs) were also similar between groups ($p = 0.63$ and $p = 0.78$, respectively) (*Tembe et al 2011*).

- Some studies have demonstrated that concurrent therapy with sodium oxybate and modafinil had a greater effect on EDS and wakefulness than either agent on its own, suggesting an additive effect (*Alshaikh et al 2012, Billiard et al 1994, Black & Houghton 2006, Black et al 2010a, Black et al 2010b, Black et al 2016, Broughton et al 1997, Kuan et al 2016, Schwartz et al 2010, Weaver et al 2006, Xyrem International Study Group 2005b).*

CLINICAL GUIDELINES

Narcolepsy:

- The 2007 AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) recommend pharmacologic therapy based on the diagnosis and targeted symptoms. Most of the agents used to treat EDS have little effect on cataplexy or other REM sleep associated symptoms, while most antidepressants and anticataplectics have little effect on alertness; however, some medications act on both symptoms. Co-administration of 2 or more drug classes may be required in some patients to adequately address their symptoms. Scheduled naps may be beneficial, but seldom suffice as primary therapy for narcolepsy. The guidelines state that modafinil is effective for treatment of EDS due to narcolepsy, and sodium oxybate is effective for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of EDS due to narcolepsy. Antidepressants (tricyclics, selective serotonin reuptake inhibitors [SSRIs], venlafaxine) may be effective for treatment of cataplexy. Tricyclics, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations.
- The European Academy of Neurology (EAN) 2011 guidelines on management of narcolepsy in adults (*Billiard et al 2011*) recommend modafinil as the first-line treatment for EDS associated with narcolepsy when EDS is the most disturbing symptom. Sodium oxybate is recommended when EDS, cataplexy, and poor sleep coexist. The guideline notes that the combination of modafinil and sodium oxybate may be more effective than sodium oxybate alone. Methylphenidate may be an option if the response to modafinil is inadequate and when sodium oxybate is not recommended. Naps are best scheduled on a patient-by-patient basis.
- While armodafinil has been shown in clinical studies to be effective for EDS in narcolepsy, its specific place in therapy is not discussed in the current guidelines.

OSA:

- The 2006 AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*) provide recommendations for patients with OSA who do not adapt well to or respond to initial therapy with continuous positive airway pressure (CPAP), oral appliances, or surgical modification. Dietary weight loss in obese individuals may be beneficial and should be combined with a primary treatment for OSA. Modafinil is recommended for the treatment of

residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.

SWD:

- The AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*) recommend planned napping before or during the night shift to improve alertness and performance in patients with SWD. Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. Modafinil is indicated to enhance alertness during the night shift for SWD. Caffeine is indicated to enhance alertness during the night shift for SWD.

SAFETY SUMMARY

- Modafinil/armodafinil:
  - Warnings and precautions of modafinil/armodafinil include rare serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); drug rash with eosinophilia and systemic symptoms (DRESS); multiorgan hypersensitivity; angioedema and anaphylaxis reactions; persistent sleepiness; psychiatric AEs; and cardiovascular AEs including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on electrocardiogram (ECG) in association with mitral valve prolapse or left ventricular hypertrophy. Increased monitoring of heart rate and blood pressure (BP) may be appropriate in patients receiving modafinil/armodafinil. Caution should be exercised when these drugs are prescribed to patients with known cardiovascular disease.
  - The most common AEs (≥ 5%) with armodafinil vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
  - The most common AEs (≥ 5%) with modafinil vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
- Pitolisant:
  - Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant is extensively metabolized by the liver, and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Pitolisant has a warning for QT prolongation. Use should be avoided with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. Patients with hepatic or renal impairment should be monitored for increased QTc.
  - In the PC trials, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
- Sodium oxybate:
  - Sodium oxybate is contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
  - Sodium oxybate carries a boxed warning concerning CNS depression and the potential for misuse/abuse. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
  - Because of the risks of CNS depression and abuse and misuse, sodium oxybate is available only through a restricted distribution program called the Xyrem REMS Program. Prescribers must be specially certified, and the drug may be dispensed only by a central pharmacy that is specially certified.
  - Other warnings and precautions include respiratory depression and sleep disordered breathing; depression and suicidality; parasomnias; and use in patients sensitive to high sodium intake due to the high salt content of sodium oxybate.
  - The most common AEs in adults (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.
  - The most common AEs in pediatric patients (≥ 5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness.
- Solriamfetol:

- ○ Solriamfetol is contraindicated with concomitant use of monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
- ○ Warnings and precautions of solriamfetol include BP and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
- ○ The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nuvigil (armodafinil)	Tablets	Oral	*Narcolepsy or OSA*: once daily in the morning. *SWD*: once daily, approximately 1 hour prior to the start of the work shift.	The dose should be reduced in patients with severe hepatic impairment and geriatric patients.
Provigil (modafinil)	Tablets	Oral	*Narcolepsy or OSA*: once daily in the morning. *SWD*: once daily, approximately 1 hour prior to the start of the work shift.	Patients with severe hepatic impairment should reduce the dose to one-half the recommended dose. Consider a lower dose in geriatric patients.
Sunosi (solriamfetol)	Tablets	Oral	*Narcolepsy or OSA:* once daily	Renal impairment: dose adjustments required; not recommended for use in patients with end-stage renal disease.
Wakix (pitolisant)	Tablets	Oral	*Narcolepsy:* once daily in the morning	Hepatic impairment: dose adjustments required in moderate impairment Renal impairment: dose adjustments required in moderate and severe renal impairment; not recommended in end stage renal disease Dose adjustments are required with concomitant use of strong CYP2D6 inhibitors, strong CYP3A4 inducers and in patients who are known CYP2D6 poor metabolizers
Xyrem (sodium oxybate)	Solution	Oral	Adults: administer nightly in 2 equal divided doses: at bedtime and 2.5 to 4 hours later; titrate to effect as directed	Both doses should be prepared prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided vials.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Pediatrics: weight-based dose administered at bedtime and 2.5 to 4 hours later; titrate to effect as directed.	Take each dose while in bed and lie down after dosing. Patients with hepatic impairment should reduce the starting dose by 50%. When using concomitantly with divalproex sodium, an initial dose reduction of at least 20% is recommended.

See the current prescribing information for full details

CONCLUSION

- Narcolepsy is a chronic neurological condition that causes excessive sleepiness throughout the day. EDS can vary in severity and in the most severe cases patients suddenly fall asleep during normal activities. Patients with narcolepsy present with or without clear evidence of cataplexy (type 1 vs type 2, respectively). There is no cure for narcolepsy, and current treatments focus on alleviating symptoms and improving quality of life.
- Current clinical evidence supports the use of modafinil as a first-line agent in treating EDS associated with narcolepsy. Sodium oxybate can be used as a second-line agent for EDS in narcolepsy, but is considered first-line therapy for patients diagnosed with cataplexy. While armodafinil has been shown in clinical studies to be effective in treating narcolepsy-associated EDS, the current clinical guidelines do not discuss a specific place in therapy. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are additional treatment alternatives for EDS due to narcolepsy, while TCAs, SSRIs, and venlafaxine are second-line alternatives for patients with cataplexy. Solriamfetol and pitolisant are potential first-line agents for narcolepsy, but they have not yet been incorporated into the guidelines. Sodium oxybate is the only agent FDA-approved for the treatment of narcolepsy in pediatric patients.
- Patients with OSA should be treated with primary CPAP therapy, and then may use modafinil, armodafinil, or solriamfetol as an adjunctive treatment for residual sleepiness.
- SWD should be treated by utilizing a planned sleep schedule, including regular naps before and during the work shift; modafinil or armodafinil may be used to enhance wakefulness in these patients.
- While current clinical data indicate that modafinil, armodafinil, pitolisant, sodium oxybate, and solriamfetol are all effective for their respective FDA-approved indications, there are a lack of head-to-head data among these agents. These agents have some differences in their AE profiles; thus, a treatment plan should be individualized for all patients and the risks and benefits should be evaluated before beginning any pharmacological therapy.
- Modafinil, armodafinil, pitolisant, and solriamfetol are oral tablets that are dosed once daily. Sodium oxybate is an oral solution that must be taken at bedtime and repeated 2.5 to 4 hours later. Currently, modafinil and armodafinil are available generically.
- Sodium oxybate carries a boxed warning for the risk of CNS depression, misuse, and abuse. Sodium oxybate is only available through the Xyrem REMS program; patients and prescribers must enroll in the program, and sodium oxybate is only dispensed through a specially certified pharmacy.
- Pitolisant does not appear to have significant abuse potential and is the only unscheduled narcolepsy agent.

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Publication Date: March 4, 2020

Prior Authorization Guideline

Guideline Name	Sickle Cell Agents

1 . Indications

Drug Name: Adakveo (crizanlizumab-tmca)
Sickle Cell Disease (to reduce frequency of vaso-occlusive crises) Adakveo is a selectin blocker indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

2 . Criteria

Product Name: Adakveo (crizanlizumab)	
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of Sickle Cell Disease

AND

2 - Patient is 16 years of age or greater [1]

AND

3 - Documentation of 2 vaso-occlusive events that required medical facility visits and

treatments in the past 12 months (e.g., sickle cell crisis, acute pain episodes, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) [1, 2]

AND

4 - Trial and failure, contraindication, or intolerance to one of the following: [3, 4, 5]

- Hydroxyurea
- L-glutamine (i.e., Endari)

AND

5 - Prescribed by or in consultation with one of the following:

- Hematologist/Oncologist
- Specialist with expertise in the diagnosis and management of sickle cell disease

Product Name: Adakveo (crizanlizumab)	
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Adakveo therapy (e.g., reduction in annual rate of vaso-occlusive events, increased time between each vaso-occlusive event)

3 . References

1. Adakveo (crizanlizumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2019.
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Prior Authorization Guideline

Guideline Name	Sickle Cell Agents

1 . Indications

Drug Name: Oxbryta (voxelotor)
Sickle Cell Disease Oxbryta is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.

2 . Criteria

Product Name: Oxbryta	
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of sickle cell disease

AND

2 - Patient is 12 years of age or greater [1]

AND

3 - Documentation of 1 vaso-occlusive crisis (VOC) event within the past 12 months (e.g., sickle cell crisis, acute painful crisis, acute chest syndrome) [2]

AND

4 - Documentation of hemoglobin level that does not exceed 10.5 g/dL prior to therapy initiation [2]

AND

5 - Trial and failure, contraindication, or intolerance to hydroxyurea [3, 4]

AND

6 - Prescribed by or in consultation with one of the following:

- Hematologist/Oncologist
- Specialist with expertise in the diagnosis and management of sickle cell disease

Product Name: Oxbryta	
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Oxbryta therapy (e.g., an increase in hemoglobin level of greater than or equal to 1 g/dL from baseline, decreased annualized incidence rate of VOCs)

AND

2 - Documentation of hemoglobin level that does not exceed 10.5 g/dL

3 . References

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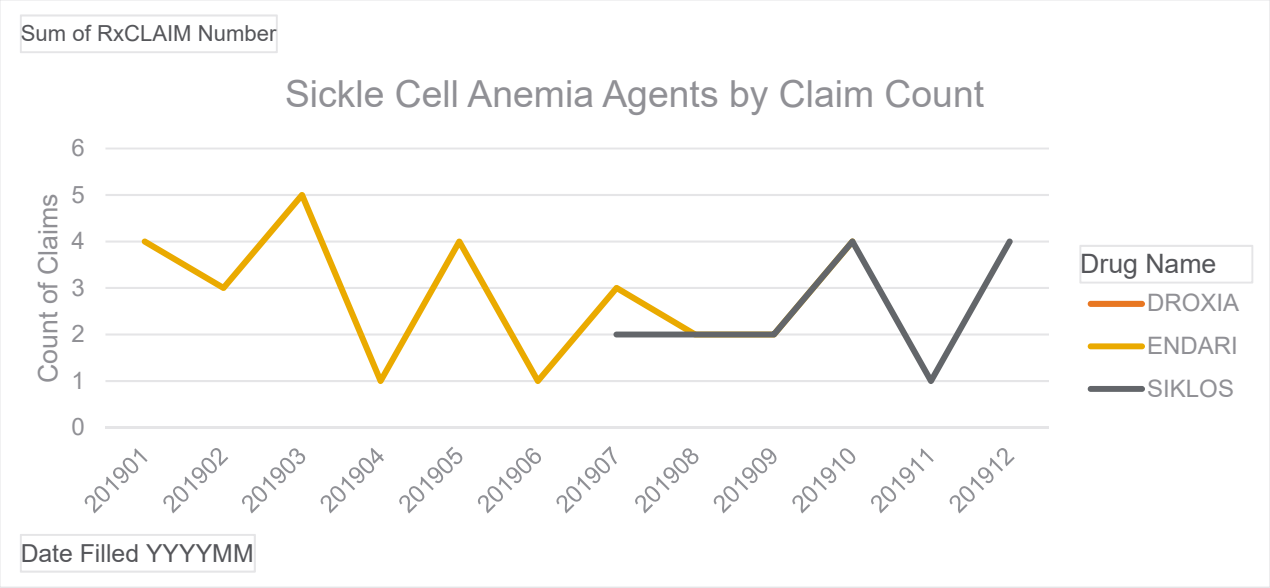
4. Brawley O, Cornelius L, Edwards L et al. National Institutes of Health Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease. Ann Intern Med. 2008;148(12):932. doi:10.7326/0003-4819-148-12-200806170-00220.

Nevada Medicaid

Sickle Cell Anemia Agents
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
SIKLOS	9	15	530	700
DROXIA	2	2	60	90
ENDARI	9	30	900	2940



Therapeutic Class Overview
Sickle cell anemia agents

INTRODUCTION

- Sickle cell disease (SCD) is a group of inherited red blood cell (RBC) disorders. The group of disorders comprising SCD is caused by a single mutation of the gene that codes for hemoglobin S (HbS), which substantially impacts the stability of the hemoglobin molecule and each RBC as a whole, as they form a sickle shape. Due to the mutation, the hemoglobin becomes more coagulable in its normal environment and cells are poor carriers of oxygen. The most common SCD genotypes include homozygous hemoglobin SS (HbSS, referred to as sickle cell anemia [SCA]) and HbS β^0-thalassemia; these genotypes are clinically similar and are associated with the most severe clinical manifestations *(National Institutes of Health [NIH] 2014, Vichinsky & Mahoney 2018)*.
- Vaso-occlusive phenomena (eg, vaso-occlusive crises [VOCs] or vaso-occlusive events [VCEs]) and hemolysis are the major clinical features of SCD (*Field & Vichinsky 2018*). Vaso-occlusion results in recurrent pain episodes (also termed sickle cell crises [SCCs]) and various organ system complications including serious infection, acute chest syndrome (ACS), renal failure, hepatobiliary complications, anemia, cerebrovascular and cardiovascular events, priapism, ocular disorders, neuropathy, and splenic sequestration that can lead to lifelong disabilities and death (*Food and Drug Administration [FDA] Multidiscipline Review [OXBRYTA] 2018, Vichinsky & Mahoney 2018*). VOC pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (*FDA Multidiscipline Review [ADAKVEO] 2018*).
- The hemoglobin level in patients with SCD is also a measure that reflects the severity and clinical course of the disease. Patients with lower hemoglobin levels (ie, anemia or hemolytic anemia) tend to have an increased risk for end-organ complications (ie, chronic kidney disease, pulmonary hypertension, stroke, and silent cerebral infarctions), and early mortality (*FDA Multidiscipline Review [OXBRYTA] 2018*). Patients may require RBC transfusions to increase hemoglobin levels.
- The exact number of people with SCD in the United States (U.S.) is unknown; it is estimated that SCD affects 100,000 Americans (*Centers for Disease Control and Prevention [CDC] Web site)*. Most of those affected are of African ancestry or self-identify as Black (*NIH 2014*). Although SCD is associated with major morbidity, currently, more than 90% of children with SCD in the U.S. and the United Kingdom survive into adulthood; however, their lifespans remain shortened by 2 or 3 decades compared to the general population.
- Hematopoietic stem cell transplantation (HSCT) and gene therapy are the only curative options for SCD; however, only a small percentage of patients are eligible for these treatment options (*FDA Multidiscipline Review [OXBRYTA] 2018*).
- Treatment options for SCD are different for each patient and depend on the symptoms *(Field & Vichinsky 2018*). In addition to lifelong supportive care (eg, RBC transfusions, pain management strategies, vaccinations, antibiotic prophylaxis) or treatment during an acute VOC (eg, pain management with non-steroidal anti-inflammatories [NSAIDs] or opioids, intravenous (IV) fluids, supplemental oxygen), patients may be placed on disease-modifying agents (*FDA Multidiscipline Review [OXBRYTA] 2018*). Currently, hydroxyurea (Droxia, Siklos, or Hydrea) is the only guideline-recommended agent for treatment of SCD (*NIH 2014*). However, L-glutamine (Endari) received FDA approval for the treatment of SCD in July, 2017. Two new agents were also recently FDA-approved for the treatment of SCD:
  - Crizanlizumab-tmca is the first targeted therapy approved for SCD, specifically inhibiting selectin (*FDA Press Release [crizanlizumab-tmca] 2019*). Crizanlizumab-tmca was granted priority review, orphan drug and breakthrough therapy designations, and was approved on November 15, 2019 (*FDA Drug Approvals and Databases Web Site [crizanlizumab-tmca])*. Crizanlizumab-tmca must fulfill post-marketing requirements and commitments, monitoring for continued safety and efficacy.
  - Voxelotor, an HbS polymerization inhibitor, was FDA approved on November 25, 2019 under accelerated approval. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Voxelotor was granted priority review, fast track, orphan drug, rare pediatric disease, and breakthrough therapy designations (*FDA Drug Approvals and Databases Web Site [voxelotor]*). Voxelotor must fulfill post-marketing requirements and commitments, monitoring for continued safety and efficacy.
- The SCD agents included in this review are listed in Table 1 by brand name. Hydroxyurea products and L-glutamine used in the treatment of SCD are excluded from this review, but are included in separate reviews.

- Medispan classes: Crizanlizumab-tmca: Agents for sickle cell anemia, selectin blocker; Voxelotor: Agents for sickle cell anemia, HbS polymerization inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adakveo (crizanlizumab-tmca)	-
Oxbryta (voxelotor)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Adakveo (crizanlizumab-tmca)	Oxbryta (voxelotor)
To reduce the frequency of VOCs in adults and pediatric patients ≥ 16 years of age with SCD	✔	
Treatment of SCD in adults and in pediatric patients 12 years of age and older*		✔

*This indication is approved under accelerated approval based on increase in hemoglobin; continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

(*Prescribing information: Adakveo 2019, Oxbryta 2019*)

- 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

- Crizanlizumab-tmca
  - The FDA approval of crizanlizumab-tmca was based on a Phase 2, multi-center (MC), double blind (DB), placebo controlled (PC), parallel group (PG), randomized controlled trial (RCT) (SUSTAIN trial) of 198 SCD patients that were randomized 1:1:1 to receive crizanlizumab-tmca 5 mg/kg, crizanlizumab-tmca 2.5 mg/kg, or placebo intravenously (IV) on weeks 0 and 2 and every 4 weeks thereafter for a total of 52 weeks (*Ataga et al 2017*). Hydroxyurea therapy was allowed if the patient was receiving it for ≥ 6 months and on a stable dose for ≥ 3 months prior to enrollment.
    - The primary endpoint was the annual rate of VOCs during the study period, defined as acute episodes of pain with no medically determined cause other than a VOC that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID. At the end of treatment, the median VOC rate per year in the intent-to-treat (ITT) population was 1.63 in the crizanlizumab-tmca 5 mg/kg group (FDA-approved dose), as compared with 2.98 in the placebo group (indicating a 45.3% lower rate with crizanlizumab-tmca than with placebo; p = 0.01). The median crisis rate in the 2.5 mg/kg crizanlizumab-tmca group was not significantly different from placebo.
    - A total of 24 of 67 patients (36%) in the crizanlizumab-tmca 5 mg/kg group and 11 of 65 patients (17%) in the placebo group had 0 VOCs during the treatment period.
    - The median time to the first VOC was significantly longer among patients receiving crizanlizumab-tmca 5 mg/kg than among those receiving placebo (4.07 vs 1.38 months, respectively; p = 0.001), as was the median time to the second VOC (10.32 vs 5.09 months, respectively; p = 0.02).
    - Assessment of quality of life (QOL) by the Brief Pain Inventory (BPI) questionnaire did not demonstrate significant changes from baseline during the trial for changes in pain severity or pain-interference.
    - Serious adverse events (SAEs) were reported in 55 patients, including 17 patients in both the crizanlizumab-tmca 5 mg/kg and placebo groups, respectively, and in 21 patients in the crizanlizumab-tmca 2.5 mg/kg treatment group. The SAEs that occurred in at least 2 patients in either crizanlizumab-tmca treatment arm and at a higher frequency than in the placebo arm were pyrexia (3% in the crizanlizumab-tmca 5 mg/kg group vs 0% in the crizanlizumab-tmca 2.5 mg/kg group vs 2% in the placebo group) and influenza (0% in the crizanlizumab-tmca 5 mg/kg group vs 5% in the crizanlizumab-tmca 2.5 mg/kg group vs 0% in the placebo group).

- Voxelotor
  - The approval of voxelotor was based on a Phase 3, MC, DB, PG, PC, RCT (HOPE trial) of 274 patients that were randomized 1:1:1 to receive either voxelotor 1500 mg, voxelotor 900 mg, or placebo orally once daily (*FDA Multidiscipline Review [OXBRYTA] 2018, Vichinsky et al 2019*). Enrolled patients had from 1 to 10 VOCs within the 12 months prior to enrollment and a baseline hemoglobin level ≥ 5.5 to ≤ 10.5 g/dL. Sixty-five percent of patients were on stable doses of hydroxyurea for at least 90 days prior to enrollment, and were allowed to continue therapy during the trial.
    - Overall, 83.9% (230 out of 274) of patients completed the study through week 24 (*FDA Multidiscipline Review [OXBRYTA] 2018*). The primary efficacy endpoint was a hemoglobin increase of > 1 g/dL from baseline to week 24. A change in hemoglobin by 1.0 g/dL is similar in magnitude to the effect of 1 unit of RBC transfusion; it is probable that an increase in hemoglobin would likely predict a decrease in stroke risk as measured by transcranial Doppler (TCD). However, verification and description of this clinical benefit is currently under investigation in confirmatory trials. The response rate for voxelotor 1500 mg (the FDA-approved dose) was 51.1% (46 out of 90), compared to 6.5% (6 out of 92) in the placebo group ($p < 0.001$).
      - The percentages of patients who underwent RBC transfusions during the trial period were similar in the 3 trial groups (33% in the voxelotor 1500 mg group, 32% in the voxelotor 900 mg group and 25% in the placebo group). Most transfusions were performed because of acute VOCs.
      - The percentages of participants who had at least 1 VOC were 67% in the voxelotor 1500 mg group, 66% in the voxelotor 900 mg group and 69% in the placebo group.
    - Secondary endpoints included the change in hemoglobin, percent change in indirect bilirubin, and percent reticulocyte count from baseline to week 24. In the voxelotor 1500 mg group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were 1.1 g/dL, -29.1%, and -19.9%, respectively. In the placebo group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were -0.1 g/dL, -3.2%, and 4.5%, respectively.
    - The most common adverse effects (AEs), with an incidence ≥ 20% were headache and diarrhea; the majority of AEs were grade ≤ 2.
    - SAEs, grade > 3 AEs, and number of patients who discontinued treatment did not differ substantially among the 3 groups. Most AEs were judged by the investigators to be unrelated to the trial drug or placebo.
    - No substantial differences in the percentages of patients who had SCD-related AEs among the treatment groups were observed (76% in the voxelotor 1500 mg treatment group and 73% in the placebo group, respectively).
    - Four deaths occurred during the trial (1 patient in the voxelotor 1500 mg group, 1 patient in the voxelotor 900 mg group, and 2 in the placebo group). None of the deaths were determined to be treatment-related.

CLINICAL GUIDELINES

- Currently in the U.S., there are no comprehensive, systematically reviewed, evidence-based guidelines for the management of SCD; however, NIH-sponsored, evidence-based expert consensus guidelines were published in 2014 *(NIH 2014)*. These guidelines provide recommendations for enhancing preventive care, managing the most common acute and chronic complications of SCD, and initiation and monitoring of the 2 available disease-modifying therapies for SCD, ie, hydroxyurea and blood transfusions. Additionally, HSCT provides hope for a cure for SCD; however, at present, the procedure is infrequently performed and very expensive. Additional research regarding patient and donor selection and the specific transplantation procedure is required before this potentially curative therapy will become more widely available.
  - Hydroxyurea and chronic blood transfusions are the 2 proven disease-modifying therapies for SCD. Both therapies are used in primary and secondary stroke prevention. Although neither has been shown to prevent all SCD-related organ damage, these treatment modalities can improve the QOL for individuals with SCD.
    - Treatment with hydroxyurea is underutilized for many people with SCA who could benefit from it. Blood transfusion therapy has at times been underutilized, overutilized, or prescribed inappropriately for both acute and chronic complications.
    - Recommendations for the use of hydroxyurea are as follows:
      - Adults with SCA who have ≥ 3 moderate to severe SCCs in a 12-month period should receive hydroxyurea (Strong recommendation, High-quality evidence).
      - Adults with SCA who have sickle cell-associated pain that interferes with daily activities and QOL should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).

- Adults with a history of severe and/or recurrent ACS should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).
- Adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities and QOL should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).
- For infants ≥ 9 months of age, children, and adolescents, treatment with hydroxyurea should be offered regardless of clinical severity to reduce SCD-related complications (Strong recommendation, High-quality evidence for age 9 to 42 months; Moderate recommendation, Moderate-quality evidence for children > 42 months and adolescents).

▪ Recommendations for blood transfusions are as follows:
- Patients with SCD should not be routinely transfused for chronic anemia or uncomplicated pain crises without an appropriate clinical indication.
- There are many potential indications for transfusion in patients with SCD. The most common indications are prophylactic perioperative transfusion; transfusion in the setting of acute occurrences such as stroke, multisystem organ failure, and ACS; and transfusion in the setting of chronic occurrences such as primary and secondary prevention of stroke in children.
  ▪ In children and adults who have had a stroke, a program of monthly simple or exchange transfusions should be initiated. (*Moderate strength, Low-Quality Evidence*)
  ▪ In children and adults who have had a stroke, if it is not possible to implement a transfusion program, hydroxyurea therapy should be initiated. (*Moderate Strength, Low-Quality Evidence*)

- The guidelines have not been updated to include the use of L-glutamine for SCD or the newly FDA-approved crizanlizumab-tmca and voxelotor. Both crizanlizumab-tmca and voxelotor may be used concomitantly with hydroxyurea.

SAFETY SUMMARY

- Voxelotor is contraindicated in patients with a prior drug sensitivity to voxelotor or excipients. Clinical manifestations may include generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia.
- Crizanlizumab-tmca has warnings and precautions for infusion-related reactions (eg, fever, chills, nausea, vomiting, urticaria, shortness of breath) and laboratory test interference (eg, platelet clumping, in particular when blood samples were collected in tubes containing ethylenediaminetetraacetic acid [EDTA]).
- Voxelotor has warnings and precautions for hypersensitivity reaction, which have occurred in < 1% of patients, and laboratory test interference with measurement of hemoglobin subtypes (ie, adult hemoglobin [HbA], sickle hemoglobin [HbS], and fetal hemoglobin [HbF]) by high-performance liquid chromatography.
- The most common AEs occurring in ≥ 10% of patients treated with crizanlizumab-tmca with a difference of > 3% compared to placebo are nausea (18%), arthralgia (18%), back pain (15%), and pyrexia (11%).
  - Clinically relevant AEs (all grades) reported in < 10% of patients included oropharyngeal pain, abdominal pain (abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, and abdominal tenderness), diarrhea, vomiting, pruritis (pruritis and vulvovaginal pruritis), musculoskeletal chest pain, myalgia, infusion-site reaction (infusion-site extravasation, infusion-site pain, and infusion-site swelling), and infusion-related reaction.
- The safety profile observed in pediatric patients 12 to < 17 years of age treated with voxelotor was similar to that seen in adult patients. The most common AEs occurring in ≥ 10% of patients treated with voxelotor with a difference of > 3% compared to placebo are headache (26%), diarrhea (20%), abdominal pain (19%), nausea (17%), fatigue (14%), rash (4%), and pyrexia (12%). Clinically relevant AEs occurring in < 10% of patients included drug hypersensitivity.
- Voxelotor also carries warnings for drug-drug interactions:
  - Co-administration of strong cytochrome P450 (CYP) 3A4 inhibitors or fluconazole may increase voxelotor plasma concentrations and may lead to increased toxicity.
  - Co-administration of strong or moderate CYP3A4 inducers may decrease voxelotor plasma concentrations and may lead to reduced efficacy.
  - Voxelotor increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate).
- Severe hepatic impairment increases voxelotor exposure, and the dose should be reduced. No dosage adjustment is required for patients with mild or moderate hepatic impairment.
- There are no available data on crizanlizumab-tmca or voxelotor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women should be

advised of the potential risk to a fetus, and crizanlizumab-tmca or voxelotor should only be used during pregnancy if the benefit of the drug outweighs the potential risk.
- There are no data on the presence of crizanlizumab-tmca or voxelotor in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for SAEs in the breastfed child, patients should be advised that breastfeeding is not recommended during treatment with either agent, and for at least 2 weeks after the last voxelotor dose.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adakveo (crizanlizumab-tmca)	Injection	IV	Loading doses: weeks 0 and 2 Maintenance doses: every 4 weeks thereafter	May be administered with hydroxyurea
Oxbryta (voxelotor)	Tablets	Oral	Once daily	May be administered with hydroxyurea Tablets should be swallowed whole, and should not be cut, crushed, or chewed Reduce dose for hepatic impairment; dose adjust for drug-drug interactions

See the current prescribing information for full details

CONCLUSION

- SCD is a serious and life-threatening chronic disorder that affects approximately 100,000 individuals in the U.S.
- SCD patients frequently experience VOCs and typically have reduced hemoglobin levels, both of which contribute to frequent hospitalizations, and significant morbidity and early mortality.
- HSCT and gene therapy are the only curative options for SCD; however, only a small percentage of patients are eligible for these treatments. Current treatment options include symptom improvement and support to decrease the number of VOCs and increase hemoglobin levels.
- Prior to the approval of crizanlizumab-tmca and voxelotor, hydroxyurea was commonly used as a potentially disease-modifying pharmacologic treatment for SCD. Per NIH consensus treatment guidelines, hydroxyurea is considered the standard of care for both adults with painful SCCs and other chronic complications, and for pediatric patients regardless of clinical severity, to reduce SCD-related complications. However, hydroxyurea may be associated with significant toxicities that include myelosuppression. L-glutamine also received FDA approval for the treatment of SCD and has shown some effectiveness in reducing VOCs; however the data remain limited. No data are available with regard to the impact of L-glutamine on mortality or QOL. Use of L-glutamine is not addressed in the NIH consensus treatment guidelines, nor are crizanlizumab-tmca or voxelotor.
- There is currently an unmet need for effective options to treat SCD. Crizanlizumab-tmca and voxelotor may provide benefit to SCD patients who are inadequately managed by other treatment options, and may be used in combination with hydroxyurea. Crizanlizumab-tmca demonstrated a lower annual rate of VOCs versus placebo. Voxelotor demonstrated a 1 g/dL increase in hemoglobin levels vs placebo but data have not shown a reduction in RBC transfusions or VOCs. Longer-term efficacy data for both agents are lacking regarding morbidity and mortality, although in clinical trials, primary endpoints were met. The overall safety profile of both agents appears manageable and acceptable for patients, although both agents are required to fulfill post-marketing requirements that continue monitoring safety and efficacy.

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Publication Date: January 22, 2020

Prior Authorization Guideline

Guideline Name	Proton Pump Inhibitors (PPI)

1 . Criteria

Product Name: All Proton Pump Inhibitors (PPIs)	
Approval Length	1 Year(s)
Guideline Type	Prior Authorization
Approval Criteria ~~**1** - Patient is not on concomitant therapy of sucralfate or an H2 antagonist~~ **AND** **2** - Patient is not exceeding once daily dosing (Quantity limit of 1 unit/day)*	
Notes	*Requests to exceed once daily dosing (QL 1 unit/day) must meet quantity limit criteria.

Product Name: All Proton Pump Inhibitors (PPIs)	
Approval Length	1 Year*
Guideline Type	Quantity Limit
Approval Criteria **1** - Requests for PPIs exceeding once per day must meet one of the following: **1.1** Patient has failed an appropriate duration of once daily dosing	

OR

1.2 Patient has one of the following diagnoses:

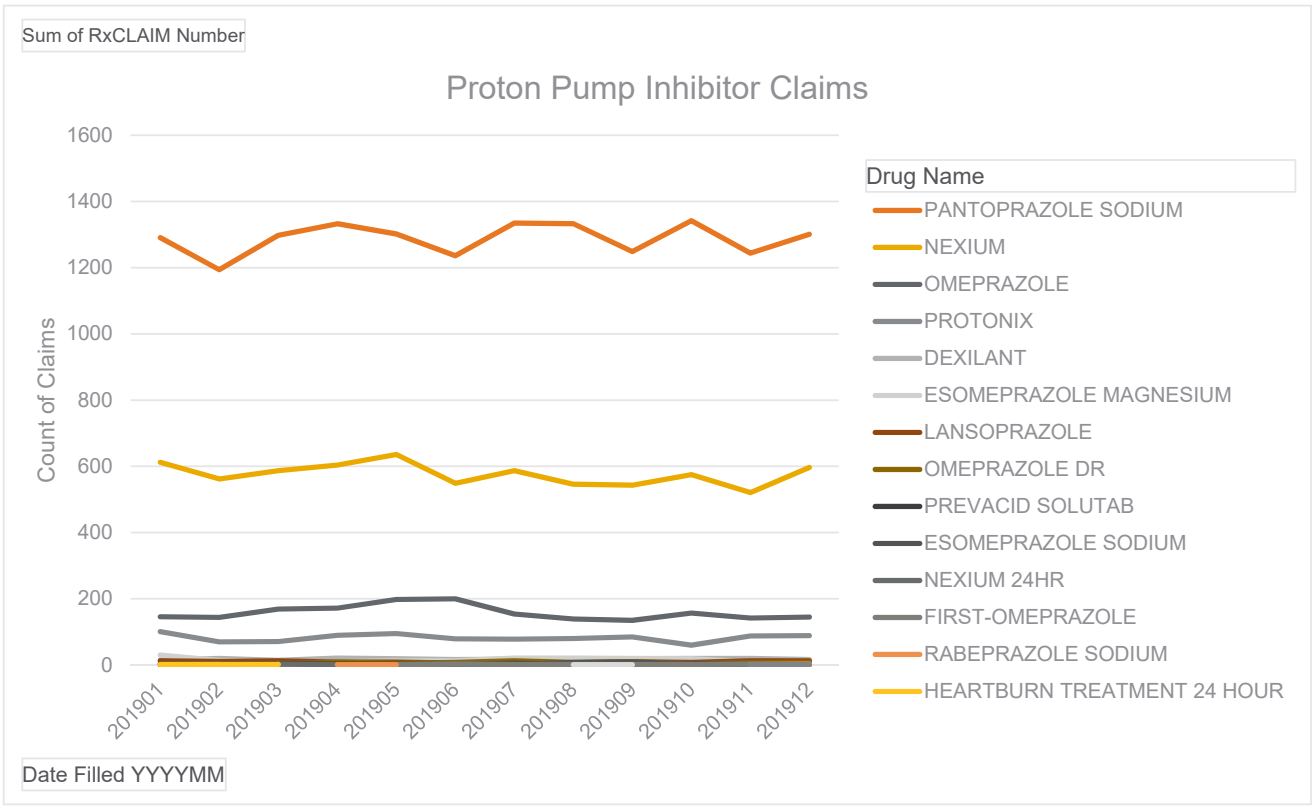
- Hypersecretory condition (e.g., Zollinger-Ellison Syndrome)
- Esophagitis
- Barrett's esophagitis
- Reflux esophagitis
- Treatment of an ulcer caused by H. Pylori

Notes	*Requests must also meet or have met any applicable drug-specific criteria for prior authorization.

Nevada Medicaid

Proton Pump Inhibitors
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
LANSOPRAZOLE ODT	1	2	60	30
FIRST-LANSOPRAZOLE	1	2	60	180
SM OMEPRAZOLE	2	2	2	3
NEXIUM	1,813	6,919	323,246	333,893
FIRST-OMEPRAZOLE	4	17	498	4,590
DEXILANT	55	215	8,247	8,487
ESOMEPRAZOLE MAGNESIUM	76	194	8,656	9,001
PROTONIX	687	986	1,532	2,060
OMEPRAZOLE DR	32	77	3,600	3,780
RABEPRAZOLE SODIUM	6	10	405	420
PREVACID	1	2	60	120
LANSOPRAZOLE	38	121	5,234	5,728
HM OMEPRAZOLE	1	1	30	30
NEXIUM I.V.	1	1	1	1
HEARTBURN TREATMENT 24 HOUR	2	7	210	210
CVS LANSOPRAZOLE	1	1	30	30
ESOMEPRAZOLE SODIUM	16	21	21	21
PANTOPRAZOLE SODIUM	5,067	15,458	545,787	557,879
OMEPRAZOLE	673	1,901	59,231	65,019
NEXIUM 24HR	5	21	774	774
PREVACID SOLUTAB	5	39	1,320	1,520



1. DRUGS REQUIRING A PRIOR AUTHORIZATION AND/OR QUANTITY LIMITATION

A. Proton Pump Inhibitors (PPIs)

Therapeutic Class: Proton Pump Inhibitor
Last Reviewed by the DUR Board: April 24, 2014

Proton Pump Inhibitors (PPIs) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Prior Authorization is not required for once per day treatment if the following criteria is met:

1. The recipient is not on concomitant therapy of an H2 antagonist or sucralfate.

b. Requests for PPIs exceeding once per day must meet one of the following:

1. The recipient has failed an appropriate duration of once daily dosing; or

2. The recipient has a diagnosis of a hypersecretory condition (e.g., Zollinger-Ellison Syndrome), esophagitis, Barrett's esophagitis, reflux esophagitis or treatment of an ulcer caused by H.Pylori.

2. Prior Authorization Guidelines

Prior authorization approval will be for up to one year.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

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 3 to 4 days (*Welage, 2003; Wolfe et al, 2000*).
- There are currently 6 PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant), esomeprazole magnesium (Nexium, Nexium IV, Nexium 24HR), 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. An alternative salt form of esomeprazole, esomeprazole strontium, was previously available, but has since been discontinued. In addition, lansoprazole, esomeprazole magnesium, omeprazole, and omeprazole with sodium bicarbonate are available over-the-counter (OTC). The only currently available PPI combination product is naproxen/esomeprazole (Vimovo); however, combination products are outside the scope of this overview and will not be reviewed.
- 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.
  - Dexlansoprazole, the enantiomer of lansoprazole, has a dual delayed-release formulation designed to provide 2 separate releases of medication. It contains 2 types of enteric-coated granules resulting in a concentration-time profile with 2 distinct peaks: the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours. In addition, it can be taken without regard to meals (*Dexilant prescribing information, 2018*).
- 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*).
- 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. Most currently available guidelines do not give preference to one PPI over another (*American Gastroenterological Association [AGA], 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2017; Moayyedi et al, 2017; Rosen et al, 2018; Shaheen et al, 2016*). The 2016 joint European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*). However, the American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD due to a lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).

- 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.
- Medispan class: Gastrointestinal Agents; Ulcer drugs/antispasmodics/anticholinergics; Proton pump inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aciphex (rabeprazole sodium) delayed-release tablets	✔
Aciphex Sprinkle (rabeprazole sodium) delayed-release capsules§	✔
Dexilant (dexlansoprazole) delayed-release capsules	-†
esomeprazole magnesium* delayed-release capsules	✔
lansoprazole* delayed-release orally disintegrating tablets	✔
Nexium (esomeprazole magnesium) delayed-release capsules	✔
Nexium (esomeprazole magnesium) granules for delayed-release oral suspension	-
Nexium IV (esomeprazole sodium) injection	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release capsules	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release tablets	-
omeprazole magnesium* delayed-release capsules, tablets, disintegrating tablet	✔
Prevacid (lansoprazole) delayed-release capsules	✔
Prevacid 24HR* (lansoprazole) delayed-release capsules	✔
Prevacid Solutab (lansoprazole) delayed-release orally disintegrating tablets	✔
Prilosec (omeprazole magnesium) oral packet	-
Prilosec OTC* (omeprazole magnesium) delayed-release tablets	✔
Protonix (pantoprazole) delayed-release tablets	✔
Protonix (pantoprazole) powder for delayed-release oral suspension	-
Protonix IV (pantoprazole) injection, powder for solution	✔
Zegerid (omeprazole with sodium bicarbonate) capsules‡	✔
Zegerid (omeprazole with sodium bicarbonate) powder for oral suspension	✔
Zegerid OTC* (omeprazole with sodium bicarbonate) capsules, oral suspension	✔

*Available OTC.
†Generic 60 mg delayed-release capsule approved by the FDA for adult patients, but generic product not yet available due to patent exclusivity.
‡A branded generic product, Omeppi, which contains the same ingredients as Zegerid capsules, is also available.
§ Generic only available in 10 mg strength

(*DRUGS@FDA.com, 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2020; Clinical Pharmacology 2020*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Dexlansoprazole	Esomeprazole magnesium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
GERD*								
Maintaining healing of erosive esophagitis	✔	✔		✔	✔	✔	✔	✔
Treatment of erosive esophagitis	✔	✔	✔	✔	✔	✔	✔ ‡	✔
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		✔ †		✔ †	✔ †			✔ †
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						✔ (oral suspension)		
Treatment of frequent heartburn for up to 14 days		✔ (Nexium 24HR)		✔ (Prevacid 24HR)	✔ (Prilosec OTC)	✔ (Zegerid OTC)		
Treatment of pathological hypersecretory conditions,		✔		✔	✔		✔ §	✔

Indication	Dexlansoprazole	Esomeprazole magnesium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
including Zollinger-Ellison syndrome								
Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults			✔					

a Esomeprazole magnesium/sodium, lansoprazole, omeprazole, pantoprazole, and rabeprazole (Aciphex Sprinkle) are approved for pediatric patients. Dexlansoprazole and rabeprazole (Aciphex) are indicated for patients 12 years of age or older. Omeprazole/sodium bicarbonate is approved for adult patients.
b As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole magnesium, 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 (7 to 10 days) of adult patients with GERD associated with a history of erosive esophagitis.
d Intravenous and oral formulation.

(*Prescribing information: Aciphex, 2019; Aciphex Sprinkle, 2018; Dexilant, 2018; lansoprazole, 2018; Nexium, 2018; Nexium IV, 2019; Nexium 24HR, 2019; Prevacid, 2018; Prevacid 24HR, 2019; Prilosec suspension, 2018; Prilosec OTC, 2019; Protonix, 2019; Protonix IV, 2019; Zegerid, 2019; Zegerid OTC, 2019*)

- 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 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[a]; Gisbert, et al, 2004[b]; 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; 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; Liang et al, 2017; 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[a]; Richter et al, 2011[b]; 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*).
- 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, 2020*).

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 2 treatments were small, and the clinical impact of the difference was not measured within the clinical trial (*Richter et al, 2001[b]*).
- The results of several meta-analyses and clinical trials demonstrated 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 4 and 8 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]; Li et al, 2017[a]; Richter et al, 2001[a]*). Subgroup analyses of 2 trials noted 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 Disease

- Meta-analyses and head-to-head trials comparing various PPIs for the treatment of peptic ulcer disease with *H. pylori* demonstrated 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[a]; Gisbert, et al 2004[b]; Ulmer et al, 2003; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007*).
- Results from 2 meta-analyses suggested that both esomeprazole- and rabeprazole-based *H. pylori* regimens were 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*).

CLINICAL 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*. Most of the treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another (*American Gastroenterological Association, 2011; Chey et al, 2017; Kahrilas et al,*

2008; Katz et al, 2013; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2017; Moayyedi et al, 2017; Rosen et al, 2018; Shaheen et al, 2016). The 2016 joint ESPGHAN/NASPGHAN guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*).

- According to the 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 alternative agents that can be used for maintenance of GERD symptoms without erosive disease (*Kahrilas, 2008; Katz et al, 2013*). The ACG medical position statement notes that there are no major differences between the different PPIs (*Katz et al, 2013*).
- According to joint recommendations from NASPGHAN and ESPGHAN (2018), PPIs are recommended as first-line therapy for the treatment of reflux-related erosive esophagitis in infants and children with GERD. For children with GERD with typical symptoms, a 4- to 8-week course of H_2-receptor antagonists or PPIs is recommended. Patients with asthma and typical GERD symptoms should also be treated (*Rosen et al, 2018*). The American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD. The 2018 guidance highlights the lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).
- 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 is 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 10 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, 2018; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] website*).
- 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

Contraindications

- Hypersensitivity to any component of their formulations
- Patients receiving rilpivirine-containing products.

Warnings and precautions

- Acute interstitial nephritis, cyanocobalamin deficiency, *Clostridium difficile*-associated diarrhea, bone fractures, hypomagnesemia, and fundic gland polyps.
- Concomitant use with clopidogrel, St. John's Wort, rifampin, high-dose methotrexate, and some antiretroviral medications (eg, protease inhibitors such as atazanavir and nelfinavir) should be avoided.
- Co-administration of PPIs with warfarin may increase international normalized ratio (INR) and prothrombin time; the dose of warfarin may need to be adjusted. False positive results for diagnostic investigations of neuroendocrine 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.
- Symptomatic response to PPI therapy does not preclude the presence of gastric malignancy.

Adverse effects

- In general, the PPIs are well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events (>2% adults).

- Long-term use of PPIs for 5 or more years has been associated with an increase in hip fractures (*Targownik et al, 2008; Islam et al, 2018; Poly et al, 2019*). When administered for 7 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*).
- 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 PPIs in 1 analysis and only with pantoprazole, lansoprazole, and esomeprazole but not with omeprazole in another (*Malhotra et al, 2018; 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*). Two recent meta-analyses of randomized controlled trials (RCTs) and observational studies found that the combined use of thienopyridines (mainly clopidogrel) and PPIs led to increases in outcomes such as recurrence of myocardial infarction, stroke, and death; however, 1 of the meta-analyses separately analyzed the results from RCTs and observational studies and found no risk difference in the RCTs. Only the observational studies pointed to an increased risk of adverse outcomes with combined use (*Pang et al, 2019*; *Khan et al, 2019)*.
- 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 2-fold increased association with cardiovascular mortality. H_2-receptor antagonists used for GERD were not associated with an increased cardiovascular risk (*Shah et al, 2015*). Another retrospective study in Taiwan found that PPI use was associated with an increased risk of hospitalization for ischemic stroke (HR, 1.36; 95% CI, 1.14 to 1.620; p = 0.001) within the 120-day period after PPI initiation (*Wang et al, 2017*). A systematic review of 6 nonrandomized observational studies directly comparing the effect of PPI use on either mortality (3 studies), and/or examining the relationship of PPI use with myocardial infarct, stroke, or peripheral arterial event determined that PPI use was associated with a higher risk for all-cause mortality (odds ratio [OR], 1.68; 95% CI, 1.53 to 1.84) and major cardiovascular events (OR, 1.54; 95% CI, 1.11 to 2.13). The rate of major cardiovascular events was also significantly higher in patients taking PPIs (OR, 1.54; 95% CI, 1.11 to 2.13, p = 0.01) (*Shiraev et al, 2018*).
  - In a large cohort study, 144,032 incident users of either PPIs or H_2-antagonists were followed for 5 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 large retrospective analysis found that PPI users had an increased risk for doubled serum creatinine levels (HR, 1.26; 95% CI, 1.05 to 1.51) and an increased risk for 30% or more decrease in estimated glomerular filtration rate (HR, 1.26; 95% CI, 1.16 to 1.36) compared to H_2-antagonist users. The risks of end-stage renal disease (HR, 2.40; 95% CI, 0.76 to 7.58) and acute kidney injury (HR, 1.30; 95% CI, 1.00 to 1.69) were also elevated with PPIs, but the risk elevations were not statistically significant. The study concluded that PPIs are associated with the risk of chronic kidney disease progression (*Klatte et al, 2017*). A retrospective analysis of claims data in Taiwan also identified an increased risk for PPI-associated chronic kidney disease in PPI-users compared to non-users (*Hung et al, 2018*). Meta-analyses evaluating the risk of chronic kidney disease have identified an increased risk for chronic kidney disease and end-stage renal disease in PPI-users as compared to both H_2-receptor antagonists-users and non-PPI users (*Nochaiwong et al, 2018; Wijarnpreecha et al, 2017*). However, these findings are based on observational studies and were deemed as low-quality evidence by Nochaiwong et al.

A prospective cohort study 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*). However, this finding has not been consistently replicated. A prospective cohort study of 13,684 patients enrolled in the Nurses' Health Study II did not find a significant association between PPI use and cognitive function after adjusting for H_2-antagonist use and other confounding variables (*Lochhead et al, 2017*). Additionally, a nested case-control study using data from the Finnish nationwide healthcare registers did not find an association between PPI use and Alzheimer's disease (OR, 1.03; 95% CI, 1.00 to 1.05) (*Taipale et al, 2017*). A prospective study analyzing Denmark survey data did not find an association between PPI use and cognitive decline (adjusted cognitive difference of 0.69; 95% CI, -4.98 to 3.61) (*Wod et al, 2018*). A prospective population-based cohort study (N = 3484) found no association between PPI use and dementia risk (HR, 0.87, 95% CI, 0.65 to 1.18 for 1 year of daily use; HR, 0.99, 95% CI, 0.75 to 1.30 for 3 years of daily use; HR, 1.13, 95% CI, 0.82 to 1.56 for 5 years of daily use) *(Gray et al*, *2018*). An observational longitudinal study found PPIs were not associated with dementia or Alzheimer's disease. Patients on continuous and intermittent therapy had a lower risk of cognitive decline (HR, 0.78, 95% CI, 0.66 to 0.93 and HR, 0.84, 95% CI, 0.76 to 0.93, respectively) (*Goldstein et al*, *2017*). A recent meta-analysis evaluated 11 observational studies (N = 642,949) and found no association between PPI use and dementia risk (adjusted HR, 1.10; 95% CI, 0.88 to 1.37) *(Khan et al 2020).*

- A recent meta-analysis found an association between gastric mucosal atrophy and long-term PPI treatment. In this analysis of 13 studies (1465 patients on long-term PPI and 1603 controls), patients on long-term PPI therapy had higher rates of gastric atrophy (OR, 1.55; 95% CI, 1.00 to 2.41) than controls. A subgroup analysis noted that omeprazole and lansoprazole groups had higher rates of gastric atrophy compared to control groups, while esomeprazole had lower rates compared to control groups (*Li et al, 2017[bj]*). An increased risk of gastric cancer with long-term use of PPIs was also demonstrated in a recent meta-analysis; 2 studies (n = 17,158 patients) provided data for this outcome (*Islam et al, 2018*). Exposure to PPIs has also been linked with an increased risk for pancreatic cancer compared to unexposed patients (OR, 1.75; 95% CI, 1.12 to 2.72) in a meta-analysis that included both interventional and observational studies (*Alkhushaym et al 2020).*
- A meta-analysis of 7 studies (N=868,882) evaluating adverse events associated with long-term use of PPIs demonstrated an increased risk of community-acquired pneumonia (OR, 1.67; 95% CI, 1.04 to 2.67) for long-term users of PPIs, older patients (> 60 years) and those who took higher doses of PPIs.; (*Islam et al, 2018*).
- A recent large factorial, double-blind, randomized trial (N = 17,585) evaluated the effectiveness of pantoprazole for preventing upper gastrointestinal bleeding in patients receiving aspirin and/or rivaroxaban. The trial randomized patients into 3 different anticoagulation strategies, as well as 1:1 for pantoprazole or placebo for gastrointestinal prophylaxis. The primary safety composite endpoint of myocardial infarction, stroke, or cardiovascular death was not different between those receiving pantoprazole versus placebo (HR, 1.04; 95% CI, 0.93 to 1.15). Additionally, no significant difference in rates of other prespecified safety outcomes were detected, which included gastric atrophy, chronic kidney disease, dementia, and pneumonia; only enteric infections were more likely to occur in pantoprazole users (OR, 1.33; 95% CI, 1.01 to 1.75) *(Moayyedi et al 2019).*

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Dexlansoprazole	Delayed-release capsule	Oral	Treatment of symptomatic, non-erosive GERD (≥ 12 years of age): Once daily for 4 weeks Treatment of erosive esophagitis (≥ 12 years of age: Once daily for up to 8 weeks	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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Maintenance of healing of erosive esophagitis (≥ 12 years of age: Once daily for up to 6 months in adults and 16 weeks in patients 12 to 17 years of age	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.
Esomeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release capsules (OTC) Delayed-release tablets (OTC)	Oral	Treatment of symptomatic GERD (≥ 12 years of age): Once daily for 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Once daily for 10 days Treatment of erosive esophagitis (≥ 12 years of age): Once daily for 4 to 16 weeks Maintenance of healing of erosive esophagitis: Once daily for up to 6 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Twice daily Risk reduction of NSAID-associated gastric ulcer: Once daily for up to 6 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	Should be taken at least 1 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 of 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 2 to 3 minutes to thicken, and drank within 30 minutes. Can also be emptied into a catheter-tipped syringe for administration via nasogastric tube. Doses > 20 mg should not be exceeded in patients with severe liver impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Treatment of symptomatic GERD, short-term (1 to 11 years of age): Once daily for up to 8 weeks Treatment of erosive esophagitis (1 to 11 years of age): Once daily for 8 weeks (weight-based) Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based)	
Esomeprazole sodium	Powder for injection	IV	Treatment of symptomatic GERD with erosive esophagitis (Adults): once daily by IV injection or IV infusion for up to 10 days Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults: IV infusion over 30 minutes followed by a continuous infusion over 3 days (72 hours) Treatment of symptomatic GERD with erosive esophagitis (1 month to 17 years of age): Once daily (weight-based) by IV infusion for up to 10 days	Should be discontinued in favor of oral therapy as soon as oral therapy is possible.
Lansoprazole	Delayed-release capsules	Oral	Treatment of symptomatic GERD	Should be taken before eating and swallowed whole.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	Delayed-release orally disintegrating tablets Delayed-release capsules (OTC) Delayed-release orally disintegrating tablets (OTC)		and heartburn (adults): Once daily for up to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 2 to 3 times daily for 10 to 14 days Treatment of active duodenal ulcers: Once daily for 4 weeks Treatment of erosive esophagitis: Once daily for up to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 8 weeks Healing of NSAID associated gastric ulcer: Once daily for 8 weeks Maintenance of healing duodenal ulcers: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Risk reduction of NSAID-associated	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 the tongue, allowed to disintegrate, and swallowed. Orally disintegrating tablets (non-OTC) 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	Available Formulations	Route	Usual Recommended Frequency	Comments
			gastric ulcer: Once daily up to 12 weeks Treatment of symptomatic GERD and erosive esophagitis (1 to 11 years of age): Once daily for up to 12 weeks (weight-based) Treatment of symptomatic nonerosive GERD (12 to 17 years of age): Once daily for up to 8 weeks Treatment of symptomatic GERD with erosive esophagitis (12 to 17 years of age): Once daily for up to 8 weeks Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release tablets and orally disintegrating tablets (OTC)	Oral	Treatment of symptomatic GERD and heartburn (adults): Once daily for 4 weeks Treatment of symptomatic GERD and erosive esophagitis due to acid-mediated GERD (1 to 16 years of age): Once daily (weight-based) for up to 4 weeks for symptomatic GERD and for up to 12 weeks for erosive esophagitis due to acid-mediated GERD	Should be taken before eating. Capsules can be opened and contents sprinkled into applesauce for immediate consumption. Unit-dose packets should be emptied into water, stirred, left for 2 to 3 minutes to thicken, and drank within 30 minutes. Capsule contents and oral suspension can also be emptied into a catheter-tipped syringe for administration via nasogastric tube.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			H. pylori eradication to reduce the risk of duodenal ulcer recurrence (adults): Once or twice daily for 10 to 14 days; an additional 10 to 18 days of therapy may be needed Treatment of active duodenal ulcers (adults): Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis due to acid-mediated GERD (adults): Once daily for 4 to 16 weeks Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based) Treatment of active, benign gastric ulcer (adults): Once daily for 4 to 8 weeks Maintenance of healing of erosive esophagitis due to acid-mediated GERD (adults): Once daily for up to 12 months Maintenance of healing of erosive esophagitis due to acid-mediated GERD (1 to 16 years of age):	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily (weight-based) for up to 12 months Note: Controlled studies do not extend beyond 12 months. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (adults): Once daily Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole/ sodium bicarbonate	Capsules Powder for oral suspension (unit-dose packets): Capsules (OTC): Note: all formulations are indicated for adults only. Their safety and effectiveness in pediatric patients < 18 years of age have not been established.	Oral	Treatment of symptomatic GERD (with no esophageal erosions): Once daily for 4 to 8 weeks Treatment of active duodenal ulcers: Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis: Once daily for 4 to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Risk reduction of	Should be taken on an empty stomach at least 1 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. 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 3 hours before and 1 hour after omeprazole/sodium bicarbonate administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			upper gastrointestinal bleeding in critically ill patients: Once daily for up to 12 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Pantoprazole	Delayed-release suspension (unit-dose packets) Delayed-release tablets Powder for injection	Oral, IV	Treatment of erosive esophagitis associated with GERD: Delayed-release suspension, delayed-release tablet: Once daily for up to 8 to 16 weeks Powder for injection: Once daily for 7 to 10 days Maintenance of healing of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release suspension, delayed-release tablet: Twice daily Powder for injection: Twice daily Treatment of erosive esophagitis (≥ 5 years of age): Delayed-release	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 1 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 2-minute or 15-minute infusion.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			suspension, delayed-release tablet: Once daily for 8 weeks	
Rabeprazole	Delayed-release tablets Sprinkle delayed-release capsules	Oral	Treatment of symptomatic GERD: Once daily for up to 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Twice daily for 7 days Healing of duodenal ulcers: Once daily after the morning meal for up to 4 weeks Healing of erosive or ulcerative GERD: Once daily for 4 to 16 weeks Maintenance of healing of erosive or ulcerative GERD: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Treatment of symptomatic GERD in adolescent patients ≥ 12 years of age: Once daily for up to 8 weeks Treatment of GERD in pediatric patients 1 to 11 years of age (Aciphex Sprinkle): Once daily for up to 12 weeks (weight-based)	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 Sprinkle capsules should be sprinkled on a spoonful of soft food or liquid, take the full dose within 15 minutes.

See the current prescribing information for full details

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 young children. Dexlansoprazole is indicated in patients ≥ 12 years of age, while omeprazole with sodium bicarbonate is only indicated in adults.
- All orally administered PPIs are available in delayed-release oral formulations, with the exception of omeprazole with sodium bicarbonate. All oral products can be dosed once daily.
- Dexlansoprazole is uniquely formulated to release at different time intervals, at 2 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. Lansoprazole and omeprazole magnesium are available as delayed-release orally disintegrating tablets.
- 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, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are all available generically, however, some formulations (eg, 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 have demonstrated 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*).
  - Richter et al reported statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known (*Richter et al, 2011[b]*).
  - 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[a]*).
  - Subgroup analyses in 2 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.
- PPIs are generally well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events. However, PPIs have been associated with a number of potential safety concerns.

- Warnings and precautions include interstitial nephritis, increased risk of *Clostridium difficile*-associated diarrhea, cyanocobalamin deficiency, hypomagnesemia, cutaneous and systemic lupus erythematosus, interactions with clopidogrel and St. John's Wort or rifampin, and increased risk of osteoporosis-related fractures with long-term use.

- 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*. Most treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another.

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Publication Date: February 19, 2020

Prior Authorization Guideline

Guideline Name	Tobacco Cessation Products

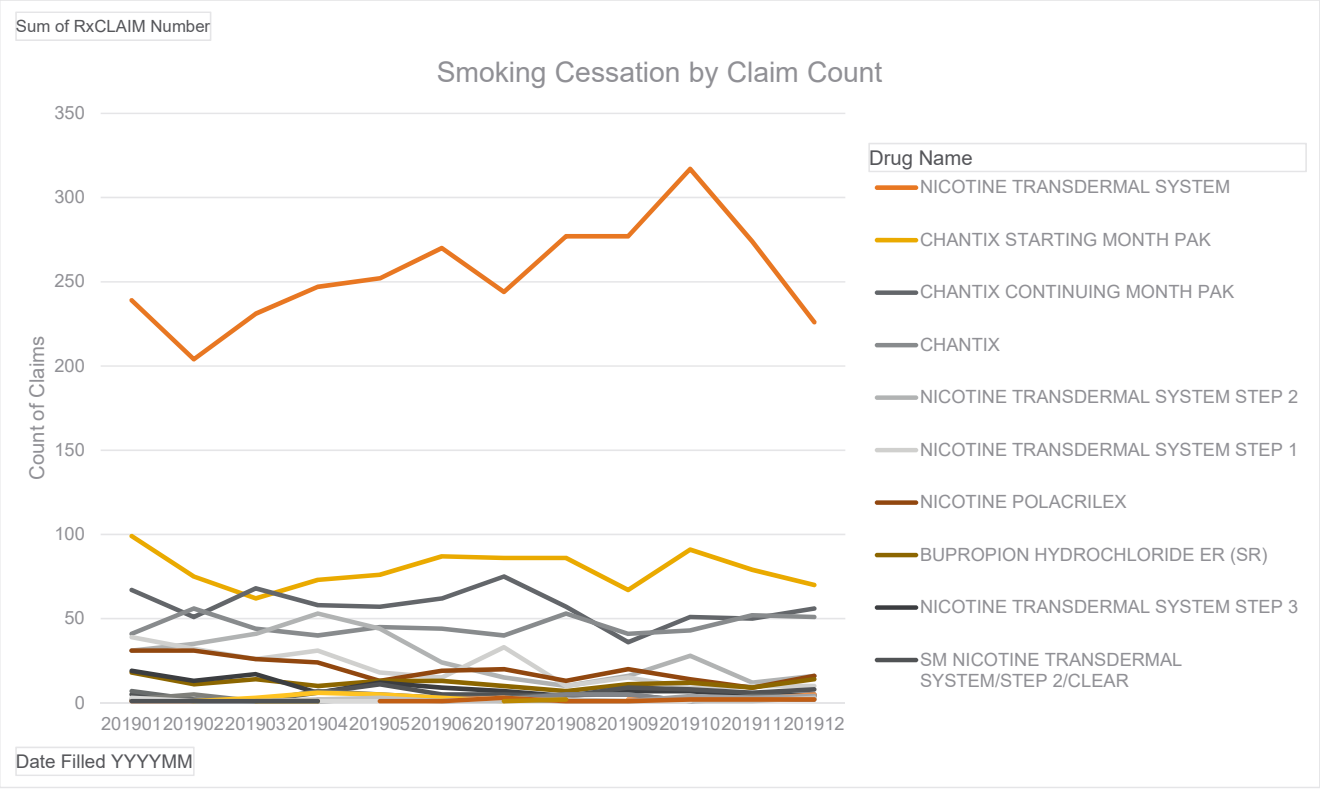
1 . Criteria

Product Name: All Tobacco Cessation Products	
Guideline Type	Quantity Limit
Smoking cessation products, including patches, gums, lozenges and inhalers (based on the recipients' route of choice), are subject to quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.	

Nevada Medicaid

Smoking Cessation Agents
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
NICOTINE TRANSDERMAL SYSTEM STEP 1	186	248	5,488	5,478
HM NICOTINE TRANSDERMAL SYSTEM	1	2	56	56
NICOTINE TRANSDERMAL SYSTEM STEP 2	261	325	7,442	7,450
SM NICOTINE TRANSDERMAL SYSTEM/STEP 3/CLEAR	17	22	476	398
NICODERM CQ	3	5	38	38
SM NICOTINE POLACRILEX	7	21	525	3,474
HM NICOTINE POLACRILEX	1	1	7	72
GNP NICOTINE TRANSDERMAL SYSTEM	14	14	322	322
SM NICOTINE TRANSDERMAL SYSTEM/STEP 1/CLEAR	34	47	1,138	1,127
NICOTINE	3	3	63	63
HM NICOTINE TRANSDERMAL SYSTEM STEP 2	3	3	70	70
NICOTROL INHALER	13	24	658	5,712
SM NICOTINE TRANSDERMAL SYSTEM	2	2	29	29
NICORELIEF	3	3	90	400
NICOTINE TRANSDERMAL SYSTEM STEP 3	89	110	2,350	2,344
CHANTIX CONTINUING MONTH PAK	351	688	20,260	39,763
NICOTINE POLACRILEX	155	236	3,930	23,935
NICOTINE TRANSDERMAL SYSTEM	1,913	3,058	61,985	62,020
BUPROPION HYDROCHLORIDE ER (SR)	77	142	4,758	8,101
GNP NICOTINE TRANSDERMAL SYSTEM STEP 2	13	16	336	336
NICORETTE	1	1	10	24
CHANTIX STARTING MONTH PAK	789	951	27,423	55,889
CHANTIX	279	550	16,939	31,548
GOODSENSE NICOTINE POLACRILEX	1	4	120	1,440
GNP NICOTINE MINI LOZENGE	1	1	21	260
NICOTROL NS	5	21	188	810
SM NICOTINE TRANSDERMAL SYSTEM/STEP 2/CLEAR	58	69	1,574	1,576
SM NICOTINE	6	15	432	3,762
GNP NICOTINE POLACRILEX	14	16	315	1,264



T. Tobacco Cessation Products

Therapeutic Class: Tobacco Cessation Agents
Last Reviewed by the DUR Board: Not Available

Smoking cessation products, including patches, gums, lozenges and inhalers (based on the recipients' route of choice), are subject to quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

Therapeutic Class Overview
Smoking Cessation Agents

INTRODUCTION

- Tobacco use is cited as the chief preventable cause of illness and death in the United States (U.S.) and is responsible for approximately 480,000 deaths each year (*National Institute on Drug Abuse [NIDA] 2020*).
- Despite the well-established adverse health consequences (eg, cardiovascular disease, multiple types of cancer, pulmonary disease, adverse reproductive outcomes, exacerbation of chronic health conditions), an estimated 34.2 million adults in the U.S. (13.7% of the adult population) currently smoke cigarettes. Passive or secondary smoke increases the risk of these adverse health consequences for nonsmokers, and increases lung cancer risk by about 20% (*Centers for Disease Control and Prevention [CDC] 2019, Department of Health and Human Services [DHHS] 2014, Fiore et al 2008, NIDA 2020*).
- E-cigarettes are currently the most commonly used tobacco product among youth, with more than 3 million (19% to 21%) high school students and 7% of 8th grade students reporting e-cigarette use in the prior month (*CDC 2018, Monitoring the Future 2019, Miech et al 2019*). E-cigarette aerosols can contain nicotine and harmful chemicals and solvents. Youth who use e-cigarettes or other tobacco products are more likely to use other tobacco products such as cigarettes (*DHHS 2016*). In 2018, the U.S. Surgeon General declared e-cigarette use among youth an epidemic (*U.S Surgeon General 2018*).
  - Recently, the CDC has reported data showing that the additive, vitamin E acetate, in some e-cigarette products is linked to e-cigarette, or vaping, product use-associated lung injury (EVALI); with more than 2600 reported cases thus far (*CDC 2020*).
- Although a high proportion of individuals express interest in quitting (currently reported at 70%), only slightly more than half of smokers make an attempt to quit (55.1% in 2018), and far fewer are successful in quitting (7.5% in 2018). Less than one-third of smokers attempting to quit report utilizing proven cessation methods such as counseling and/or medication (*CDC 2019*).
- Although some individuals are able to quit unaided, strong evidence is available showing that smokers are significantly more likely to quit successfully if they use evidence-based counseling or medication treatment than if they try to quit without such aids. First-line Food and Drug Administration (FDA)-approved pharmacologic interventions include nicotine replacement therapy (NRT), bupropion hydrochloride (HCl) sustained-release (SR), and varenicline. All first-line therapies are indicated as aids to smoking cessation treatment (*Fiore et al 2008, Siu et al 2015*).
- Studies have compared the effects of the first-line pharmacotherapies when administered as monotherapy or combination therapy. Multiple systematic reviews and meta-analyses have also been published evaluating the safety and efficacy of pharmacotherapy as an aid to smoking cessation.
- Over-the-counter (OTC) NRT products include nicotine gum, lozenge, and patch. Prescription NRT products include nicotine nasal spray and nicotine inhalation system. Chantix (varenicline) is a prescription partial nicotine agonist that prevents nicotine stimulation of the dopamine system and decreases craving and withdrawal symptoms. Zyban (bupropion HCl SR) is a prescription dopamine/norepinephrine-reuptake inhibitor; its ability to enhance tobacco cessation is not fully understood. The above mentioned agents will be discussed in this review.
- Medispan Class: Smoking Deterrents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Chantix (varenicline)	-
Nicoderm CQ (nicotine extended-release) transdermal patch*	✔
Nicorette (nicotine polacrilex) gum*	✔
Nicorette (nicotine polacrilex) lozenge*	✔
Nicotrol (nicotine) inhalation system	-
Nicotrol NS (nicotine) nasal spray	-
Zyban (bupropion HCl sustained-release)†	✔

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020)*

*OTC products
†Brand Zyban was discontinued, but a generic version remains available.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication*	Chantix (varenicline)	Nicoderm CQ (nicotine extended-release) transdermal patch	Nicorette (nicotine polacrilex) gum	Nicorette (nicotine polacrilex) lozenge	Nicotrol (nicotine) inhalation system	Nicotrol NS† (nicotine) nasal spray	Zyban (bupropion HCl SR)
To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking		✔	✔	✔			
As an aid to smoking cessation for the relief of nicotine withdrawal symptoms					✔	✔	
As an aid to smoking cessation treatment	✔						✔

*All tobacco cessation agents should be used as part of a comprehensive behavioral smoking cessation program.
†The safety and efficacy of the continued use of NICOTROL NS for periods longer than 6 months have not been adequately studied and such use is not recommended.

(Prescribing information: *Bupropion HCl SR 2019, Chantix 2019, Nicoderm CQ 2018, Nicorette gum 2018, Nicorette lozenge 2018, Nicotrol 2019, Nicotrol NS 2019*)

- 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

Comparative Efficacy of Pharmacologic Treatments

- A systematic review of 54 systematic reviews/meta-analyses, sponsored by the Agency for Healthcare Research and Quality (AHRQ), found that behavioral and pharmacotherapy interventions improved rates of smoking cessation among the general adult population, alone or in combination (*Patnode et al 2015*).
  - NRT might increase smoking abstinence at 6 months follow-up or longer by 53% to 68% (risk ratio [RR] 1.60; 95% confidence interval [CI], 1.53 to 1.68; I^2 = 30%; N = 51,265), bupropion SR by 49% to 76% (RR 1.62; 95% CI, 1.49 to 1.76; I^2 = 18%; N = 13,728), and varenicline by 102% to 155% (RR 2.27; 95% CI, 2.02 to 2.55; I^2 = 63%; N = 6166) compared to placebo or no NRT.
  - Absolute cessation differences averaged 7% for NRT, 8.2% for bupropion SR, and 16% for varenicline.
  - No differences were found among NRT products (eg, patch, gum, lozenge).
  - Use of a combination of NRT products increased cessation rates more than the use of a single NRT product (20.6% vs 5%, respectively; RR 1.34; 95% CI, 1.18 to 1.51; I^2 = 34%; N = 4664).
  - Combined behavioral interventions and pharmacotherapy also increased cessation rates at ≥ 6 months after the start of treatment vs control groups (14.5% vs 8.3%, respectively; RR 1.82; 95% CI, 1.66 to 2.00; N = 15,021).
- A Cochrane review of 12 published Cochrane reviews (N = 101,804) demonstrated the efficacy of NRT, bupropion, and varenicline in improving the chances of quitting smoking. Based on network meta-analysis, the following findings were observed for sustained smoking cessation ≥ 6 months from the start of treatment (*Cahill et al 2013*):

  - Both NRT (odds ratio [OR] 1.84; 95% CI, 1.71 to 1.99) and bupropion (OR 1.82; 95% CI, 1.60 to 2.06) were superior to placebo. Varenicline more than doubled the chances of quitting compared to placebo (OR 2.88; 95% CI, 2.40 to 3.47).
  - Direct comparisons between bupropion and NRT suggested equal efficacy with no advantage for either treatment (OR 0.99; 95% CI, 0.86 to 1.13).
  - Varenicline was shown to be superior to both NRT (OR 1.57; 95% CI, 1.29 to 1.91) and bupropion (OR 1.59; 95% CI, 1.29 to 1.96) monotherapy. However, varenicline was not more effective than combination NRT (OR 1.06; 95% CI, 0.75 to 1.46).
  - Binary meta-analysis of the results demonstrated that bupropion combined with NRT was not more effective than NRT alone (RR 1.23; 95% CI, 0.67 to 2.26).
- Three systematic reviews/meta-analyses of randomized controlled trials (RCTs) found all pharmacologic treatments (ie, NRT, bupropion, varenicline) to be significantly more effective than controls in assisting with smoking cessation up to 12 months after the target quit date. Varenicline was the only pharmacotherapy that demonstrated consistent effectiveness over other treatment options (*Eisenberg et al 2008, Mills et al 2012, Wu et al 2006*).
- A large, multi-center, double-blind (DB), placebo-controlled (PC) and active-controlled (AC) RCT demonstrated the safety and efficacy of varenicline and bupropion vs nicotine patch and placebo in patients with psychiatric disorders. A total of 8144 patients (4116 in psychiatric cohort; 4028 in non-psychiatric cohort) were randomized in a 1:1:1:1 fashion to receive varenicline, bupropion, nicotine patch, or placebo for 12 weeks. The primary endpoint was incidence of moderate and severe neuropsychiatric events. The primary efficacy endpoint was smoking abstinence for weeks 9 to 12 (*Anthenelli et al 2016*).
  - In the psychiatric cohort, moderate and severe neuropsychiatric events were reported in 6.5% of patients in the varenicline group, 6.7% of the bupropion group, 5.2% of the nicotine patch group, and 4.9% of the placebo group. The varenicline and bupropion vs placebo risk differences (RD) for these neuropsychiatric events were 1.59 (95% CI, -0.42 to 3.59) and 1.78 (95% CI, -0.24 to 3.81), respectively. The RD for varenicline and bupropion vs nicotine patch were 1.22 (95% CI, -0.81 to 3.25) and 1.42 (95% CI, -0.63 to 3.46), respectively.
  - In the non-psychiatric cohort, moderate and severe neuropsychiatric events were reported in 1.3% of patients in the varenicline group, 2.2% of the bupropion group, 2.5% of the nicotine patch group, and 2.4% of the placebo group. The varenicline and bupropion vs placebo RD for these neuropsychiatric events were -1.28 (95% CI, -2.4 to -0.15) and -0.08 (95% CI, -1.37 to 1.21), respectively. The RD for varenicline and bupropion vs nicotine patch were -1.07 (95% CI, -2.21 to 0.08) and 0.13 (95% CI, -1.19 to 1.45), respectively.
  - Higher abstinence rates were achieved in varenicline-treated patients compared to all other treatment arms. Compared with placebo, the bupropion and nicotine patch groups also achieved higher abstinence rates.
  - The results of this trial did not indicate a significant increase in moderate or severe neuropsychiatric events in patients with or without psychiatric disorders treated with varenicline or bupropion relative to nicotine patch or placebo.
- A DB, triple-dummy, PC and AC, RCT (N = 8058) comparing the cardiovascular safety risk of smoking cessation treatments (varenicline, bupropion, NRT) found that the incidence of major adverse cardiovascular events (MACE) during treatment and follow-up was low (< 0.5%) and did not differ significantly by treatment. There were no significant differences for any drug vs placebo in terms of time to cardiovascular event, blood pressure, or heart rate (*Benowitz et al 2018*).
- A meta-analysis of 32 randomized, DB, PC trials evaluated sex differences between bupropion, transdermal nicotine (TN) and varenicline for smoking cessation (N = 14,398); 51% of patients were female. Overall, all medications improved quit rates vs placebo for both women and men. However, significant sex differences were evident when comparing varenicline vs TN and varenicline vs bupropion. For women, varenicline was more efficacious than TN (RR 1.41; 95% CI, 1.12 to 1.76) and bupropion (RR 1.38; 95% CI, 1.08 to 1.77). For men, outcomes were similar across all 3 medications. There were no differences in efficacy when comparing bupropion versus TN. Authors concluded that the advantage of varenicline over bupropion SR and TN is greater for women than men (*Smith et al 2017*).

Efficacy of Combination Therapy vs Monotherapy

- A DB, PC, RCT (N = 385) was conducted at a hospital-based outpatient clinic to evaluate the efficacy of varenicline and bupropion combination therapy vs varenicline alone for smoking cessation. Patients were given 12 weeks of treatment and were followed for 12 months. The combination group failed to demonstrate superiority vs the varenicline alone group in terms of prolonged abstinence at 12 months (OR 0.91; 95% CI, 0.50 to 1.64). Both treatment groups were superior to placebo (p < 0.016) (*Cinciripini et al 2018*).

- A large Phase 4, open-label (OL), RCT was conducted in 2 counties in Wisconsin to determine the comparative efficacy of nicotine patch (N = 241), varenicline (N = 424), and combination nicotine patch plus nicotine lozenge (combination NRT) (N = 421) on biochemically confirmed abstinence at 26 weeks. Pharmacotherapy was administered at standard doses for 12 weeks. Results demonstrated that there were no significant differences in point prevalence abstinence rates among the 3 groups at 26 weeks (nicotine patch, 22.8%; varenicline, 23.6%; and combination NRT, 26.8%) or at 52 weeks (nicotine patch, 20.8%; varenicline, 19.1%; and combination NRT, 20.2%). No significant treatment effects were found between groups for prolonged abstinence rate (nicotine patch 14.9%, varenicline 16.5%, combination NRT 15.4%) (*Baker et al 2016*).
- Another Phase 4, OL, RCT conducted at a single center in Canada evaluated the comparative smoking cessation effects of standard nicotine patch administered for 10 weeks (NRT; N = 245), extended use of nicotine patch plus nicotine gum or inhaler administered for up to 22 weeks (combination NRT; N = 245), and varenicline 1 mg twice daily administered for up to 24 weeks (N = 247). Overall, combination NRT and varenicline were found to enhance success in the early phases of quitting. Varenicline improved abstinence in the medium-term; however, there was no clear evidence that either varenicline or combination NRT increased quit rates in the long-term when compared to NRT monotherapy. No differences in continuous abstinence rates were observed between treatment groups from weeks 5 to 52 (10.0%, 12.4%, and 15.3% in the NRT, combination NRT, and varenicline groups, respectively). However, both combination NRT and varenicline had statistically significantly higher continuous abstinence rates over NRT monotherapy from weeks 5 to 10 (unadjusted OR 1.52; 97.5% CI, 1.00 to 2.30, and OR 1.58; 97.5% CI, 1.04 to 2.39, respectively), and varenicline had higher continuous abstinence rates over NRT at weeks 5 to 22 (unadjusted OR 2.01; 97.5% CI, 1.20 to 3.36) (*Tulloch et al 2016*).
- The efficacy of combination nicotine patch with other pharmacotherapy (ie, nicotine gum, nicotine inhaler, nicotine nasal spray, bupropion HCl SR) compared to monotherapy or placebo was evaluated in a meta-analysis of 5 RCTs (N = 2204). Abstinence rates were significantly higher with combination therapy than monotherapy at 3 months (39.0% vs 27.6%, respectively; RR 1.42; 95% CI, 1.21 to 1.67), 6 months (29.3% vs 19.1%, respectively; RR 1.54; 95% CI, 1.19 to 2.00), and 12 months (22.2% vs 14.3%, respectively; RR 1.58; 95% CI, 1.25 to 1.99). Adverse events (AEs) and adherence to combination therapy were similar to monotherapy and placebo (*Shah et al 2008*).
- A Cochrane systematic review of 63 studies (N = 41,509) comparing at least 2 NRT regimens found a higher rate of abstinence at 6 months with combination NRT therapy compared to monotherapy (RR 1.25, 95% CI, 1.15 to 1.36, 14 studies, 11,356 participants) *(Lindson et al 2019).*

Antidepressants

- A Cochrane systematic review of 90 RCTs (N > 27,000) assessed the efficacy of antidepressants in aiding long-term smoking cessation. Both bupropion and nortriptyline were more effective than placebo (bupropion: RR 1.62; 95% CI, 1.49 to 1.76; nortriptyline: RR 2.03; 95% CI, 1.48 to 2.78). There was no evidence of significant effects with other antidepressant therapies. Bupropion and nortriptyline appeared equally effective, although the comparison trended toward favoring bupropion (RR 1.30; 95% CI, 0.93 to 1.82). Bupropion had significantly lower abstinence rates compared to varenicline (RR 0.68; 95% CI, 0.56 to 0.83). There were no direct comparisons between nortriptyline and varenicline (*Hughes et al 2015*).

Nicotine Replacement Therapies

- A Cochrane systematic review of 136 studies (N = 64,640 in main analysis) found that all forms of NRT (gum, transdermal patch, intranasal spray, and sublingual tablets/lozenges) significantly increased the rate of smoking cessation compared to placebo or no NRT control. The RR for abstinence for any form of NRT compared to control was 1.55 (95% CI, 1.49 to 1.61). The effects were largely independent of the definition of abstinence, the intensity of additional support provided, or the setting in which the NRT was offered. In a subset of 6 trials in pregnant women, NRT had a statistically significant benefit on abstinence close to the time of delivery (RR 1.32; 95% CI, 1.04 to 1.69); however, the result was no longer statistically significant in the 4 trials that followed patients post-partum (*Hartmann-Boyce et al 2018*).
- Pooled results from a meta-analysis comparing long-term studies (2 to 8 years, weighted mean 4.3 years) of single-course NRT vs control (12 RCTs, N = 4792) found that the long-term benefit of NRT is modest, and tobacco dependence treatment might be better viewed as a chronic disorder requiring repeated episodes of treatment. Abstinence rates were similar after 1 year of follow-up (OR 2.13; 95% CI, 1.68 to 2.69) and after more than 1 year of follow-up (OR 1.99; 95% CI, 1.50 to 2.64). The overall relapse rate between 12 months and final follow-up was 30.0%. The relapse rate did not differ by time of final follow-up, suggesting that most relapses after 12 months occur in the

following 1 to 2 years. Due to relapse, the estimated overall net benefit of NRT over and above placebo declined from 10.7% after 1 year to 7.2% at a mean of 4.3 years of follow-up (*Etter et al 2006*).

Varenicline

- A recent Cochrane review of 42 studies (N = 27,537) evaluated the safety and efficacy of varenicline for smoking cessation (*Cahill et al 2016*).
  - Pooled data from 27 trials indicated that standard-dose varenicline (1 mg twice daily for 12 weeks) increased the chances of successful long-term smoking cessation between 2- and 3-fold compared to placebo (RR 2.24; 95% CI, 2.06 to 2.43).
  - Extended varenicline treatment beyond 12 weeks was well tolerated and demonstrated a clear benefit over placebo (RR 3.64; 95% CI, 2.81 to 4.72; 4 trials).
  - Similar to other systematic reviews/meta-analyses, varenicline demonstrated significantly greater efficacy over bupropion (RR 1.39; 95% CI, 1.25 to 1.54) and NRT (RR 1.25; 95% CI, 1.14 to 1.37).
- In a meta-analysis of 5 RCTs (N = 2292), longer courses of varenicline treatment significantly improved the likelihood of successful smoking cessation. A significant relationship was found between the length of exposure to varenicline and abstinence rates (β coefficient, 0.5% absolute increase in abstinence rate per week of exposure; 95% CI, 0.3 to 0.8%; $p < 0.0001$). The unadjusted abstinence rates for 6-, 12-, and 24-weeks of varenicline treatment were 14.4%, 22.4%, and 43.6%, respectively (*Lee et al 2008*).
- A meta-analysis of 3 RCTs (N = 904) found combination therapy with varenicline and NRT to be more effective than varenicline alone in achieving smoking abstinence before or at the end of treatment (44.4% vs 35.1%, respectively; OR 1.50; 95% CI, 1.14 to 1.97), and after the end of treatment (32.4% vs 23.1%, respectively; OR 1.62; 95% CI, 1.18 to 2.23). The incidence of AEs was similar between the 2 treatment groups. Patients receiving combination therapy reported slightly more nausea (28.4% vs 25.7%), insomnia (18.7% vs 15.4%), and abnormal dreams (13.6% vs 10.7%) vs varenicline monotherapy (*Chang et al 2015*).
- Varenicline has a warning for the potential for serious cardiovascular events to occur. Previous meta-analyses have provided conflicting results regarding these events. A recent meta-analysis of 38 RCTs (N = 12,706) found no difference in serious cardiovascular events with varenicline vs placebo (RR 1.03; 95% CI, 0.72 to 1.49). Findings were similar when comparing patients with and without cardiovascular disease (RR 1.04; 95% CI, 0.57 to 1.89; RR 1.03; 95% CI, 0.64 to 1.64, respectively). No difference was detected in all-cause mortality between the varenicline and placebo groups (RR 0.88; 95% CI, 0.5 to 1.52) (*Sterling et al 2016*).

CLINICAL GUIDELINES

U.S. Public Health Service – Treating Tobacco Use and Dependence (*Fiore et al 2008*)

- The combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. Therefore, whenever feasible and appropriate, both counseling and medication should be provided to patients trying to quit smoking.
- Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations for which there is insufficient evidence of effectiveness (ie, pregnant women, smokeless tobacco users, light smokers, and adolescents)
- All NRT, bupropion SR, and varenicline are considered first-line treatment options and reliably increase long-term smoking abstinence rates.
- Certain combinations of first-line medications have been shown to be effective smoking cessation treatments. Therefore, clinicians should consider using these combinations of medications with their patients who are willing to quit. Effective combination medications are:
  - Long-term (> 14 weeks) nicotine patch + other NRT (gum and spray)
  - Nicotine patch + nicotine inhaler
  - Nicotine patch + bupropion SR (only combination approved by the FDA)

U.S. Preventive Services Task Force (USPSTF) – Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women (*Siu et al 2015*)

- Clinicians should ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral and FDA-approved pharmacotherapy for cessation.
- Nonpregnant adults ≥ 18 years:
  - Pharmacotherapy and behavioral intervention should be provided for cessation.

  - Behavioral therapy alone or combined with pharmacotherapy substantially improves achievement of tobacco cessation.
  - Use of NRT, bupropion, or varenicline with or without behavioral therapy substantially improves achievement of tobacco cessation. Using 2 types of NRT moderately improves achievement of tobacco cessation over using 1 type. The addition of NRT to bupropion SR provides benefit over use of bupropion SR alone.
- Pregnant women ≥ 18 years:
  - Behavioral interventions should be provided for cessation.
  - Behavioral interventions substantially improve achievement of tobacco smoking abstinence, increase infant birthweight, and reduce risk for preterm birth.
  - There is inadequate or no evidence on the benefits of NRT, bupropion SR, or varenicline to achieve tobacco cessation in pregnant women or improve perinatal outcomes in infants; the balance of benefits and harms cannot be determined.

National Comprehensive Cancer Network (NCCN) – Smoking Cessation (*NCCN 2019*)
- Treatment plans for all patients should include a combination of motivational/behavioral strategies and pharmacotherapy. Behavioral strategies include brief counseling and ≥ 4 individual or group therapy sessions (preferred).
- The most effective pharmacotherapy options are varenicline and NRT. A trial of varenicline or combination NRT (transdermal patch plus lozenge, gum, or inhaler) for 12 weeks should be attempted as primary therapy, and this can be continued for 6 to 12 months if needed.
- Relapse can be managed by restarting the treatment used for primary therapy or trying the other therapy.
- Bupropion alone or in combination with NRT can be considered as a subsequent therapy option. Bupropion should not be used in patients with brain metastases.
- Varenicline-associated nausea should be carefully managed in patients with cancer, especially those receiving concurrent chemotherapy.

American Academy of Pediatrics – Clinical Practice Policy to Protect Children From Tobacco, Nicotine, and Tobacco Smoke (*Farber et al 2015)*
- Clinicians should ask about tobacco use, including e-cigarette use, during all visits with children or adolescents.
- Parent and caregiver tobacco use should also be addressed and tobacco dependence treatment offered.
- Adolescents who want to stop smoking should be offered tobacco dependence treatment, which can include pharmacotherapy (any medication that is FDA-approved for tobacco dependence in adults) for moderate to severe dependence.
- Electronic nicotine delivery devices (such as e-cigarettes) should not be offered to adolescents with tobacco dependence.
- Telephone/text quitline referral and other behavioral interventions can also be considered for adolescents.

American College of Cardiology (ACC) Expert Consensus Decision Pathway on Tobacco Cessation Treatment (*Barua et al 2018*)
- The pathway is a systematic stepwise guide for addressing cigarette smoking efficiently and effectively during a routine office-based appointment.
  1. Ask about and document every patient's tobacco use status and exposure to secondhand smoke at every visit using a standardized assessment method.
  2. Assess current smokers' degree of nicotine addiction, former smokers' risk of relapse, and all nonsmokers exposure to secondhand smoke.
  3. Advise all tobacco users to quit, emphasizing the personal benefits of cessation rather than the harms of continuing to smoke, and advise all nonsmokers to avoid secondhand smoke exposure.
  4. Offer and connect smokers to appropriate treatment options (prescribing pharmacotherapy and actively linking smokers to behavioral support available in their healthcare institution or in the community.
  5. Follow up with patients at subsequent visits to monitor smoking status and sustain engagement in smoking cessation treatments as needed.

- Pharmacotherapy should act synergistically with behavioral counseling to increase quit rates.
  - The first-line pharmacotherapy recommendations for smoking cessation, including in smokers with cardiovascular disease, are varenicline and combination NRT.
  - NRT monotherapy and bupropion are considered second-line options for patients with cardiovascular disease who are not able or willing to use first-line choices.

SAFETY SUMMARY

Boxed Warnings:

- Suicidality and antidepressant drugs: Although bupropion HCl SR (Zyban) is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin, Wellbutrin SR, and Wellbutrin XL. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. Patients of all ages who are started on antidepressant therapy should be monitored closely for worsening, and for emergence of, suicidal thoughts and behaviors.
- The FDA recently removed the boxed warning for serious mental health AEs from the Chantix and Zyban drug labels based on results from a large clinical trial. The risk of serious AEs on mood or behavior was found to be lower than previously thought. Although the risk of mental AEs in patients with current or history of mental illness is still present, most did not have serious consequences (ie, hospitalization). The benefits of smoking cessation outweigh the risks with these medications (*FDA Safety Communication 2016, FDA Safety Oversight Meeting 2017*).

Contraindications:

- Bupropion HCl SR is contraindicated in seizure disorders, history of anorexia or bulimia, or patients undergoing abrupt cessation of ethanol or sedatives; concurrent or recent (within 14 days) use of monoamine oxidase inhibitors (MAO-Is) is also contraindicated.
- Varenicline is contraindicated in patients with a known history of serious hypersensitivity or skin reactions to varenicline. There have been postmarketing reports of rare, potentially life-threatening skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients treated with varenicline. Patients should contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.
- Nicotine polacrilex lozenges contain soya. Patients who are allergic to soya should not use this formulation.

Warnings/Precautions:

- Serious neuropsychiatric reactions (eg, changes in mood [including depression and mania], psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide) have been reported in patients taking bupropion for smoking cessation and in patients taking varenicline. These events have occurred in patients with and without pre-existing psychiatric disease. Patients should be instructed to discontinue the drug and to contact a healthcare provider if they experience such AEs.
- Both bupropion HCl SR and varenicline have a risk of seizures. These medications should be used with caution in patients with a history of seizures or other factors that can lower the seizure threshold.
- Bupropion HCl SR can cause hypertension, precipitate a manic or hypomanic episode in patients with bipolar disorder or risk factors for bipolar disorder, and trigger an angle-closure attack in patients with angle-closure glaucoma.
- Nicotine can increase heart rate and blood pressure. The risk of nicotine replacement in patients with cardiovascular and peripheral vascular disease should be weighed against the benefits of including NRT in a smoking cessation program. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed. Nicotine inhaler/nasal spray generally should not be used in patients during the immediate post-myocardial infarction period, or in patients with serious arrhythmias or severe/worsening angina.
- NRT should be used with caution in patients with hyperthyroidism, hepatic or renal impairment, insulin-dependent diabetes, and patients with active peptic ulcer disease, as healing may be delayed.
- Nicotine nasal spray is not recommended for use in patients with chronic nasal disorders. Bronchospasm has been reported in patients with pre-existing asthma with use of both nicotine nasal spray and inhaler. Sustained use beyond 6 months with these products is not recommended.
- Varenicline may cause central nervous system (CNS) depression that may impair physical or mental abilities. Caution must be used when performing tasks that require mental alertness. Varenicline may also change the way patients react to alcohol; alcohol intake should be decreased until patients know how it is tolerated. Cases of somnambulism (sleep walking) have been reported with use of varenicline involving harmful behavior to self, others, or property.

- An evaluation of the cardiovascular risk with varenicline suggests that patients with underlying cardiovascular disease may be at increased risk; however, these concerns must be balanced with the health benefits of smoking cessation. A trial in patients with stable cardiovascular disease demonstrated that while cardiovascular events were infrequent overall, some nonfatal events were reported more frequently in patients treated with varenicline. All-cause and cardiovascular mortality was lower in patients treated with varenicline. A meta-analysis of 15 trials found an increased hazard ratio for MACE of 1.95, but the finding was not statistically significant. In a large postmarketing neuropsychiatric safety outcome trial, few MACE events occurred.
- Nausea is the most common AE (up to 30% incidence rate) reported in patients treated with varenicline. It has been generally described as mild or moderate and often transient; however, it may persist over several months for some patients. The incidence of nausea is dose-dependent; initial dose titration may be beneficial in reducing the occurrence of nausea, and dose reduction for patients with intolerable nausea should be considered.
- Efficacy of varenicline has not been demonstrated in pediatric patients. Use of varenicline is not recommended for patients ≤ 16 years of age.
- Pregnancy and Lactation
  - Available data have not suggested an increased risk for major birth defects following exposure to varenicline in pregnancy, compared with women who smoke. There are no data on the presence of varenicline in human milk; the benefits of breastfeeding should be considered along with the mother's clinical need for the drug and any potential AEs on the breastfed child or from the underlying maternal condition.
  - Women who are pregnant should be encouraged not to smoke. The use of NRT to aid in smoking cessation has not been adequately studied in pregnant women; nonpharmacologic treatments are recommended. The amount of nicotine in breast milk from replacement products varies; caution should be exercised when nicotine is administered to breast-feeding women (*Facts & Comparisons 2018*).
  - Bupropion HCl SR is pregnancy category C. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant smokers should be encouraged to attempt cessation using nonpharmacological approaches first. Bupropion and its metabolites are present in human milk; caution should be exercised when it is administered to a nursing woman.

AEs:

- The most common AEs (incidence ≥ 5%) for bupropion HCl SR are insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia.
- The most common AEs for nicotine polacrilex gum/lozenges are injury to mouth, teeth, or dental work; belching; increased salivation; mild jaw muscle ache; and sore mouth/throat.
- The most common AEs for the nicotine transdermal patch are transient and generally mild erythema, pruritus, or burning at the application site.
- The most common AEs for the nicotine inhaler and nasal spray include local irritation of the mouth, throat, or nose; cough; dyspepsia; and headache. Nasal irritation was reported by nearly all (94%) patients treated with nicotine nasal spray during the first 2 days in a PC trial. Both the frequency and severity of nasal irritation declined with continued use, but was still experienced by 81% of patients after 3 weeks of nicotine nasal spray treatment. Most patients rated nasal irritation as mild or moderate.
- The most common AEs (incidence ≥ 5%) for varenicline are nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Chantix (varenicline)	Tablets	Oral	Once daily for 3 days, then twice daily	Dosing should begin 1 week prior to quit date. Alternatively, varenicline can be initiated with a later quit date set between days 8 and 35 of treatment. An additional 12 weeks of treatment is recommended if successful cessation

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				is achieved after the first 12-week course to further increase the likelihood of long-term abstinence. Administer after eating and with a full glass of water. Dosage adjustment is recommended for severe renal impairment and end-stage renal disease (ESRD).
Nicoderm CQ (nicotine extended-release)	Transdermal patch	Transdermal	Once daily	The patch is designed to be worn for 24 hours and then removed. The used patch should be removed and a new one applied to a different site at the same time each day. Hands should be washed after application or removal of a patch. The patch should be applied to any hairless site, avoiding areas with cuts, breakouts, scars, oil, burns, or irritation. The patch should not be cut in half or into smaller pieces.
Nicorette (nicotine polacrilex)	Gum	Oral	Weeks 1 to 6: 1 piece every 1 to 2 hours; Weeks 7 to 9: 1 piece every 2 to 4 hours; Weeks 10 to 12: 1 piece every 4 to 8 hours Maximum: 24 pieces/day	Patients should chew nicotine gum slowly until a tingling sensation in the mouth occurs, then park gum between cheek and gum. When tingling is gone, begin chewing again until tingle returns and repeat process until tingle is gone (about 30 min). Eating and drinking should be avoided 15 min before using and while gum is in mouth. The gum should not be swallowed.
Nicorette (nicotine polacrilex)	Lozenge	Oral	Weeks 1 to 6: 1 lozenge every 1 to 2 hours; Weeks 7 to 9: 1 lozenge every 2 to 4 hours; Weeks 10 to 12: 1 lozenge every 4 to 8 hours Maximum: 5 lozenges/6 hours or 20	Patients should place the lozenge in the mouth and allow to slowly dissolve. The lozenge should occasionally be moved from one side of the mouth to the other until completely dissolved (about 20 to 30 minutes). Eating and drinking should be avoided 15 min before using and while lozenge is in mouth.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			lozenges/day	The lozenge should not be chewed or swallowed.
Nicotrol (nicotine)	Inhalation system (cartridge)	Inhaled	6 to 16 cartridges per day for up to 12 weeks, then gradual reduction of dose for 6 to 12 weeks Maximum: 16 cartridges/day	A cartridge is inserted into the inhaler before use; the patient should inhale deeply into the back of the throat or puff in short breaths. The nicotine in each cartridge is used up after about 20 minutes of active puffing.
Nicotrol NS (nicotine)	Nasal spray	Intranasal	Initial: 1 spray (0.5 mg) in each nostril 1 or 2 times/hour Maximum: 40 doses (80 sprays)	Patients should be encouraged to use at least the recommended minimum of 8 doses per day, as less is unlikely to be effective. Patients should not sniff, swallow or inhale through the nose as the spray is being administered. Patients should be advised to administer the spray with the head tilted back slightly Maximum recommended duration of treatment: 3 months
Zyban (bupropion HCl sustained-release)	Tablets	Oral	Once daily for 3 days, then twice daily	Tablets should be swallowed whole and should not be crushed, divided, or chewed. May be taken with or without food. Dosing should begin 1 week before quit date. Dose adjustment is recommended for moderate to severe hepatic impairment. Dosage adjustment should be considered for mild renal and hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Tobacco use is the primary avoidable cause of illness and death in the U.S., leading to approximately 480,000 deaths each year. Almost 50 million adults in the U.S. use tobacco on a regular basis. Cardiovascular disease, cancers, pulmonary disease, and adverse reproductive outcomes are all well-known adverse health consequences of tobacco use (*CDC 2019, Fiore et al 2008, NIDA 2020*).
- Less than 1 in 10 smokers are successful in quitting, but strong evidence indicates that smokers are significantly more likely to successfully quit if behavioral therapy and/or tobacco cessation medication is used. NRT, bupropion HCl SR, and varenicline are all effective first-line medication therapies. Nicotine gum, lozenges, and patches are available OTC.

Nicotine inhalation and nasal spray, bupropion SR, and varenicline are prescription products (*CDC 2017, Fiore et al 2008, Siu et al 2015*).

- Meta-analyses comparing NRT, bupropion SR, and varenicline have found all to be efficacious in aiding smoking cessation. Data suggest that varenicline monotherapy may be more effective than NRT or bupropion monotherapy (*Cahill et al 2013, Eisenberg et al 2008, Mills et al 2012, Patnode et al 2015, Wu et al 2006*).
- Meta-analyses have shown statistically significantly better abstinence rates in smokers using combination therapy with multiple NRT products or NRT plus bupropion SR or varenicline (*Chang et al 2015, Lindson et al 2019, Shah et al 2008, Stead et al 2012*).
- Bupropion HCl SR (Zyban), although only used as a smoking cessation therapy, shares a boxed warning with other antidepressant drugs that it may increase the risk of suicidal thoughts and behaviors in children, adolescents, and young adults. Bupropion is contraindicated in patients with seizure disorders.
- NRT can cause increased heart rate and blood pressure; risk vs benefit should be weighed in patients with cardiovascular and peripheral vascular disease. NRT should be used with caution in patients with hyperthyroidism, hepatic or renal impairment, insulin-dependent diabetes, and patients with peptic ulcer disease. The most common AEs are local irritation related to product application site and are typically mild in nature.
- Varenicline may cause CNS depression, neuropsychiatric effects, and an increased risk of cardiovascular events. Nausea is the most common AE and is typically dose-dependent.
- Current guidelines from the U.S. Public Health Service, USPSTF, NCCN, and the American Academy of Pediatrics recommend that health professionals encourage all patients to quit smoking and to provide behavioral therapy and/or FDA-approved tobacco cessation medication when appropriate. A combination of behavioral therapy with tobacco cessation medication is significantly more effective than monotherapy. NRT, bupropion HCl SR, and varenicline are all considered first-line and efficacious in adults (*Fiore et al 2008, Siu et al 2015, NCCN 2019, Farber et al 2015*). The American Academy of Pediatrics does not provide specific pharmacotherapy recommendations for tobacco cessation in adolescents but states that use of these products can be considered (*Farber et al 2015*).

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Prior Authorization Guideline

Guideline Name	Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

1. Indication

Drug Name: Toradol (ketorolac tromethamine) tablets
Pain management (acute; moderately severe): Short-term (≤5 days) management of moderate to severe acute pain

2 . Criteria

Product Name: **Toradol (ketorolac tromethamine) tablets**	
Approval Length	Up to 5 Days
Guideline Type	Prior Authorization

Approval Criteria

1 – Both of the following

1.1 Oral treatment is indicated only as continuation therapy to IV/IM therapy.

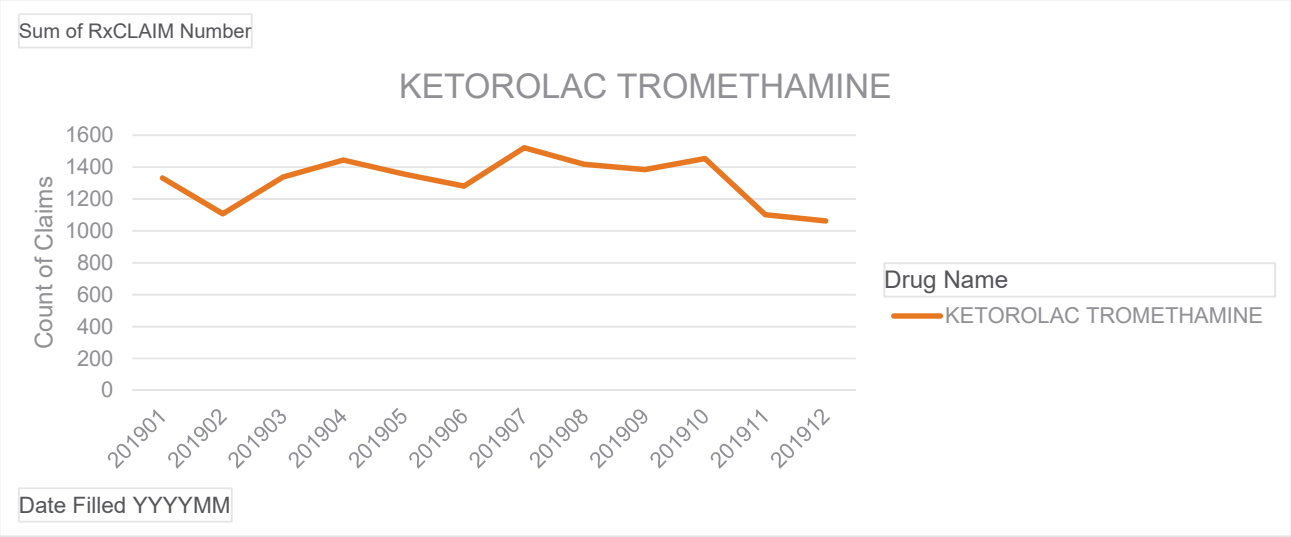
AND

1.2 Oral treatment is not to exceed five days.

Nevada Medicaid

Ketorolac
Fee for Service
January 1, 2019 - December 31, 2019

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
KETOROLAC TROMETHAMINE	9,717	15,800	18,932	40,751



R. Toradol® (ketorolac tromethamine) tablets

Therapeutic Class: Nonsteroidal Anti-inflammatory Drugs, NSAIDS
Last Reviewed by the DUR Board: Not Available

The pharmaceutical Toradal® is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Ketorolac is indicated for the short-term (up to five days) management of moderately severe acute pain that requires analgesia at the opioid level. It is not indicated for minor or chronic painful conditions. The following criteria must be met:

a. Oral treatment is indicated only as continuation therapy to IV/IM therapy.

b. Oral treatment is not to exceed five days.

2. Prior Authorization Guidelines

The prior authorization must be initiated by the prescriber. The approved prior authorization must be available if requested.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

INTRODUCTION

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large class of medications with analgesic, anti-inflammatory, and anti-pyretic properties used for a wide variety of conditions including pain, rheumatoid arthritis (RA), osteoarthritis (OA), primary dysmenorrhea, ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), acute migraine, and acute gout *(Conaghan 2012).*
  - RA is an autoimmune inflammatory arthritis that is treated with conventional, biologic, or targeted small molecule disease-modifying antirheumatic drugs (DMARDs) such as Trexall (methotrexate), tumor necrosis factor (TNF) inhibitors, non-TNF biologics, or Janus kinase inhibitors. Analgesics, including NSAIDs, have a limited role in most patients with active disease, but may be considered as a temporary adjunctive option. *(Moreland et al 2020, Singh et al 2015).*
  - OA is the most common form of arthritis, and is a degenerative inflammatory disease that can be pharmacologically treated with oral or topical NSAIDs, intraarticular (IA) glucocorticoid injections, acetaminophen, duloxetine, topical capsaicin, and tramadol *(Kolasinski et al 2020).*
  - Primary dysmenorrhea is menstrual pain in the absence of other pelvic pathology, and represents one of the most common causes of pelvic pain. It can be treated with oral NSAIDs, hormonal contraceptives, complementary and alternative therapies, and exercise *(ACOG 2018, Osayande et al 2013).*
  - AS is a chronic inflammatory arthritis characterized by sacro-iliac joint involvement that can be treated with NSAIDs, TNF inhibitors, sulfasalazine, methotrexate, tofacitinib, secukinumab, ixekizumab, locally administered glucocorticoids, physical therapy, or surgery *(Ward et al 2016, Ward et al 2019).*
  - JIA is a chronic idiopathic inflammatory disorder that affects pediatric patients. JIA encompasses multiple forms of arthritis in childhood, including what was previously described as juvenile rheumatoid arthritis before being supplanted by the newer term. Treatment for JIA includes conventional or biologic DMARDs, intravenous immunoglobulin, calcineurin inhibitors, IA glucocorticoids, and NSAIDs *(Grom 2018, Ringold et al 2013, Ringold et al 2019).*
  - Migraine is a disorder associated with severe headaches worsened by activity, light, and/or sounds, and can be treated with oral analgesics including NSAIDs and opioids, ergot derivative medications, triptans, antiemetics, and antiepileptics *(Marmura et al 2015, Oskoui et al 2019).*
  - Gout is the most common cause of inflammatory arthritis in adults, and typically presents acutely as synovitis due to tissue deposition of monosodium urate crystals. Acute gout can be treated with Colcrys (colchicine), systemic corticosteroids, and/or NSAIDs *(Khanna et al 2012, Qaseem et al 2017).*
- Some NSAIDs including ibuprofen and naproxen are available at lower strengths as over-the-counter (OTC) formulations, which do not require a prescription. The same compounds are also available in higher strengths as a prescription-only product. Other NSAIDs are available only by prescription regardless of strength.
- Both prescription-strength and OTC NSAIDs are widely utilized, accounting for over 111 million prescriptions annually and 60% of the OTC analgesic market in the United States (U.S.). The use of NSAIDs has been increasing over time and utilization is highest in individuals over 60 years of age *(Conaghan 2012, Davis et al 2017).*
- The therapeutic effects of NSAIDs are primarily attributed to inhibition of cyclooxygenase (COX) enzymes, which participate in the formation of mediators associated with inflammation and pain. Most NSAIDs block both related isoforms of the COX enzyme: COX-1 and COX-2 *(Solomon 2017).*
  - COX-1 regulates normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. Inhibition of COX-1 is theorized to contribute to some adverse events associated with NSAID use *(Solomon 2017).*
  - COX-2 is usually undetectable in most tissues, but its expression is increased during states of inflammation. For patients with a high risk for GI events, a selective COX-2 inhibitor may be preferred over a nonselective NSAID. Gastroprotective agents are also available to reduce the risk of NSAID-associated GI events. These agents include an exogenous prostaglandin (misoprostol), histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs) *(Solomon 2017).*

- In 2005, the Food and Drug Administration (FDA) began requiring all prescription NSAIDs to carry a boxed warning highlighting the potential for increased risk of cardiovascular (CV) events such as myocardial infarction (MI) and stroke, as well as gastrointestinal (GI) bleeding. OTC NSAIDs were also required to have labeling providing more specific information about these risks *(FDA Drug Safety Communication).*
  - In 2015, following an advisory committee review of additional evidence, the FDA required revisions to existing warnings for both prescription and OTC NSAIDs to strengthen messaging regarding potential risks of use. Statements were included regarding the risk potentially increasing with duration of use *(FDA Drug Safety Communication).*
- Most NSAIDs on the market have been generic for some time. In fact, many of the originator brand products have been discontinued, leaving only generic versions on the market. The newer patented NSAIDs Cambia (diclofenac potassium), Durlaza (aspirin ER), Qmiiz ODT (meloxicam), Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) are new formulations of previously approved molecular entities manufactured at a new strength, dosage form, and/or delivery system.
- This review includes an evaluation of orally administered, single-agent, prescription NSAIDs. Products that are available OTC are included if they are also available in a prescription-only strength or formulation.
- Medispan class: Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anaprox DS (naproxen sodium)	✔
Cambia (diclofenac potassium)	-
Celebrex (celecoxib)	✔
Daypro (oxaprozin)	✔
diclofenac	✔
diclofenac potassium	✔
diclofenac sodium DR	✔
diclofenac sodium ER	✔
diflunisal	✔
Durlaza (aspirin ER)	-
EC-Naprosyn (naproxen DR)	✔
etodolac	✔
etodolac ER	✔
Feldene (piroxicam)	✔
flurbiprofen	✔
ibuprofen	✔
Indocin (indomethacin)	✔ *
indomethacin ER	✔
ketoprofen	✔
ketoprofen ER	✔ †
ketorolac	✔
Lodine (etodolac)	✔
Meclofen (meclofenamate)	✔ †
Mefenam (mefenamic acid)	✔
Mobic (meloxicam)	✔
nabumetone	✔
Nalfon (fenoprofen)	✔
Naprelan (naproxen sodium SR)	✔
Naprosyn (naproxen)	✔
Qmiiz ODT (meloxicam)	-

Drug	Generic Availability
Relafen DS (nabumetone)	-
sulindac	✔
Tivorbex (indomethacin)	-
tolmetin	✔
Vivlodex (meloxicam)	-
Zipsor (diclofenac potassium)	-
Zorvolex (diclofenac)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)
*Only capsule formulation is available generically; the oral suspension and rectal suppository are branded products only.
†Available as a single-source generic product.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Anaprox DS (naproxen sodium)	✔	✔	✔	✔	✔	• Polyarticular juvenile idiopathic arthritis • Tendonitis or bursitis • Acute gout
Cambia (diclofenac potassium)						• Acute treatment of migraine
Celebrex (diclofenac potassium)	✔	✔	✔	✔	✔	• Juvenile RA
Daypro (oxaprozin)		✔	✔			• Juvenile RA
diclofenac or diclofenac potassium	✔	✔	✔	✔		
diclofenac sodium DR		✔	✔		✔	
diclofenac sodium ER		✔	✔			
diflunisal	✔	✔	✔			
Durlaza (aspirin ER)						• Reduce risk of death and MI in patients with chronic coronary artery disease • Reduce risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA
EC-Naprosyn (naproxen DR)		✔	✔		✔	• Polyarticular juvenile idiopathic arthritis
etodolac	✔ †	✔	✔			
etodolac ER		✔	✔			• Juvenile RA
Feldene (piroxicam)		✔	✔			
flurbiprofen		✔	✔			
ibuprofen	✔	✔	✔	✔		• Reduction of fever* • Juvenile RA*

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Indocin (indomethacin)		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
indomethacin ER		✔	✔		✔	• Acute painful shoulder
ketoprofen	✔	✔	✔	✔		
ketoprofen ER		✔	✔			
ketorolac						• Moderately severe acute pain‡
Meclofen (meclofenamate)	✔	✔	✔	✔	✔	• Reduction of fever • Juvenile RA • Acute painful shoulder • Acute gouty arthritis • Idiopathic heavy menstrual blood loss
Mefenam (mefenamic acid)	✔ §			✔		
Mobic (meloxicam)		✔	✔			• Juvenile RA
nabumetone		✔	✔			
Nalfon (fenoprofen)	✔	✔	✔			
Naprelan (naproxen sodium SR)	✔	✔	✔	✔	✔	• Tendonitis or bursitis • Acute gout
Naprosyn (naproxen)	✔	✔	✔	✔	✔	• Polyarticular juvenile idiopathic arthritis • Tendonitis or bursitis • Acute gout
Qmiiz ODT (meloxicam)		✔	✔			• Juvenile RA
Relafen DS (nabumetone)		✔	✔			
sulindac		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
Tivorbex (indomethacin)	✔ †					
tolmetin		✔	✔			• Juvenile RA
Vivlodex (meloxicam)			✔			
Zipsor (diclofenac potassium)	✔ †					
Zorvolex (diclofenac)	✔ †		✔			

*Indications for prescription oral suspension only†Acute pain only
‡Acute pain only, treatment limited to 5 days of total therapy
§Acute pain only, when therapy will not exceed 7 days
(*Prescribing information: Anaprox DS, EC-Naprosyn, Naprosyn 2019, Cambia 2019, Celebrex 2019, Daypro 2019, diclofenac potassium 2017, diclofenac sodium DR 2017, diclofenac sodium ER 2017, diflunisal 2016, Durlaza 2015, etodolac 2016, etodolac ER 2016, Feldene 2019, flurbiprofen 2017, ibuprofen 2019, ibuprofen suspension 2019, Indocin 2019, indomethacin ER 2019, ketoprofen 2018, ketoprofen ER 2019, ketorolac 2015, meclofenamate 2019, mefenamic*

acid 2020, Mobic 2018, nabumetone 2016, Nalfon capsule 2016, Nalfon tablet 2018, Naprelan 2019, Naprosyn 2019, Qmiiz ODT 2019, Relafen DS 2019, sulindac 2019, Tivorbex 2020, tolmetin capsule 2015, tolmetin tablet 2015, Vivlodex 2019, Zipsor 2019, Zorvolex 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

- Generally, the NSAID class has well-established efficacy as analgesic and anti-inflammatory medications. In addition to placebo-controlled pivotal trials for individual agents, several systematic reviews and meta-analyses have shown that NSAIDs compare favorably to placebo for pain reduction for various conditions. Most have also concluded that there is insufficient evidence that any one NSAID is more effective than any other *(Derry et al 2012, Enthoven et al 2016, Kroon et al 2015, Marjoribanks et al 2015, Wang et al 2016).*
  - A Cochrane review of NSAIDs for treatment of chronic low back pain evaluated 13 trials (N = 1354), and concluded that there is evidence that NSAIDs are more effective than placebo at reducing pain and disability. No difference in efficacy was seen between individual NSAIDs *(Enthoven et al 2016).*
  - A systematic review (N = 68 trials) of NSAID use in various types of chronic pain including OA, RA, soft-tissue pain, back pain, and AS found that there are no significant differences in pain relief between nonselective NSAIDs, partially selective NSAIDs (defined in the trial as meloxicam, nabumetone, and etodolac), and celecoxib. Comparisons between nonselective NSAIDs also found no clear differences in efficacy *(Peterson et al 2010).*
  - In a comparative effectiveness review, the Agency for Healthcare Research and Quality (AHRQ) assessed the efficacy of selective and non-selective NSAIDs, aspirin, acetaminophen, OTC supplements (chondroitin and glucosamine), and topical NSAIDs and rubefacients for treatment of OA. The review found that good evidence exists that nonselective NSAIDs do not differ significantly in efficacy for pain relief as compared to each other or to COX-2 selective NSAIDs *(Chou et al 2011).*
  - A Cochrane review including 80 trials (N = 5820) concluded that NSAIDs are a very effective treatment for primary dysmenorrhea. Insufficient evidence was found to determine if any individual NSAID is more effective than another NSAID, including comparisons between COX-2 selective and nonselective NSAIDs *(Marjoribanks et al 2015).*
  - A network meta-analysis of 26 trials (N = 3410) for treatment of pain due to AS found that there were no significant differences in efficacy between NSAIDs. Etoricoxib (an NSAID not available in the U.S.) was found to be superior to celecoxib, ketoprofen, and tenoxicam (also not available in the U.S.). No other significant differences between NSAIDs were found. All 20 evaluated NSAIDs reduced pain as compared to placebo *(Wang et al 2016).*
  - A systematic review of 39 studies (N = 4356) evaluating the use of NSAIDs for axial spondyloarthritis determined that there is high to moderate quality evidence that NSAIDs are efficacious for treatment of axial spondyloarthritis. NSAIDs were more beneficial than placebo and there was no difference in efficacy between the various evaluated NSAIDs, including COX-2 selective agents *(Kroon et al 2015).*
  - A Cochrane review of NSAIDs for treatment of acute gout including 23 trials (N = 2200) determined that while data is insufficient to draw firm conclusions, they do not conflict with guideline recommendations for the use of NSAIDs as first-line treatment. Additionally, moderate-quality evidence was found to support the claim that COX-2 selective NSAIDs and nonselective NSAIDs are probably equally beneficial *(van Durme et al 2014).*
- Comparative reviews have also been conducted evaluating the efficacy of oral NSAIDs as compared to topical NSAIDs and other non-NSAID agents for the treatment of various types of pain.
  - A Cochrane review of 34 studies (N = 7688) evaluated oral NSAIDs and topical diclofenac for treatment of OA pain. The review found that while both were significantly more effective than placebo, there appeared to be no difference in efficacy between the two treatment modalities for knee or hand OA *(Derry et al 2012).*
  - A network meta-analysis of 137 studies (N = 33,243) comparing acetaminophen, oral NSAIDs, and IA injections of corticosteroids or hyaluronic acid concluded that IA treatments were clinically superior to oral NSAIDs after 3 months of treatment. Oral NSAIDs were in turn clinically superior to acetaminophen for treatment of OA pain after the same duration of treatment *(Bannuru et al 2015).*
  - For treatment of OA, AHRQ has stated that topical and oral NSAIDs were found to have similar efficacy, although topical NSAIDS were associated with a lower risk of GI complications and a higher risk of dermatologic adverse events *(Chou et al 2011).*

- A network meta-analysis found that select NSAIDs (celecoxib, diclofenac, naproxen, and piroxicam) and opioids are similarly effective in reduction of pain for the treatment of knee OA *(Smith et al 2016).*
- A network meta-analysis comparing ibuprofen, diclofenac potassium, aspirin, and multiple triptans (including a combination of naproxen and sumatriptan) for treatment of migraine found that ibuprofen and aspirin were inferior to eletriptan and rizatriptan with respect to pain relief, but that diclofenac potassium was more effective than any other intervention for pain relief at 2 hours. However, diclofenac did have the largest rate of migraine recurrence requiring rescue therapy. Addition of naproxen to sumatriptan significantly reduced the rate of migraine recurrence as compared to sumatriptan alone. Overall tolerability was similar between the NSAIDs, which as a class was superior to that of the triptans *(Xu et al 2016).*
- A Cochrane review concluded that for primary dysmenorrhea, the NSAID class appears to be more effective than acetaminophen. However, this analysis was based on only 3 trials that compared NSAIDs with acetaminophen, and the quality of evidence was low *(Marjoribanks et al 2015).*
- A meta-analysis of 3 studies (N = 584) comparing oral prednisolone to oral NSAIDs for treatment of acute gout found similar efficacy between the agents *(Yu et al 2018)*.
- The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial evaluated the CV safety of celecoxib 100 to 200 mg twice daily compared with ibuprofen 600 to 800 mg 3 times daily and naproxen 375 to 500 mg twice daily. The randomized, multicenter, DB, noninferiority trial included 24,081 patients with increased CV risk who required NSAID therapy for OA or RA. The primary outcome measure was a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcome measures included GI and renal safety (*Nissen et al 2016*).
  - Celecoxib was noninferior to ibuprofen and naproxen with regards to CV safety. In the intent-to-treat population, a primary outcome event occurred in 2.3% of the celecoxib group, 2.5% of the naproxen group, and 2.7% of the ibuprofen group (hazard ratio [HR], 0.93 vs naproxen; HR, 0.85 vs ibuprofen; $p < 0.001$ for noninferiority to both).
  - Celecoxib was associated with a lower incidence of GI AEs compared to naproxen ($p = 0.01$) and ibuprofen ($p = 0.002$).
  - Celecoxib was also associated with a significantly lower incidence of renal AEs compared with ibuprofen ($p = 0.004$). Statistical significance was not reached when compared with naproxen ($p = 0.19$).

- Studies were conducted evaluating the efficacy of Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) as compared to placebo. All 3 products were found to be superior to placebo for the treatment of pain in individual randomized controlled trials. Studies were not conducted comparing efficacy or safety of these products vs existing higher-dose generic formulations of indomethacin, meloxicam, or diclofenac. Systemic exposure of Tivorbex, Vivlodex, and Zorvolex has not been shown to be equivalent to other formulations of oral indomethacin, meloxicam, and diclofenac, respectively.
- Qmiiz ODT (meloxicam) is an orally disintegrating tablet (ODT) that was approved based on a single-dose pharmacokinetic study that established equivalence between the 15 mg ODT tablet and meloxicam (Mobic) 15 mg tablet (*Radicioni et al 2013*).
- Several large systematic reviews and meta-analyses have analyzed the risk of adverse events with use of NSAIDs, including comparisons between the nonselective NSAIDs and between nonselective and COX-2 selective NSAIDs.
  - A large meta-analysis of 280 trials (N = 124,513) evaluating the CV and GI risk of various NSAIDs concluded that the vascular risk of high-dose diclofenac (150 mg daily or greater) and possibly ibuprofen are comparable to that of COX-2 selective NSAIDs. By contrast, high-dose naproxen (100 mg daily or greater) is associated with less vascular risk than other NSAIDs. All NSAIDs increased risk of upper GI complications by a factor of 2 to 4, although the lowest incidence was seen with COX-2 selective NSAIDs. None of the evaluated NSAIDs were found to increase risk of stroke *(Coxib and traditional NSAID Trialists' [CNT] Collaboration 2013).*
  - A Bayesian meta-analysis of MI risk with NSAID use in a cohort of 446,763 individuals found that all NSAIDs, including naproxen and celecoxib, were associated with an increased risk of acute MI. Risk was greatest with use of higher doses as well as during the first month of NSAID use. Risk did not appear to increase beyond the first 30 days of use *(Bally et al 2017).*
  - A comparative effectiveness review found that there were important safety differences among different NSAIDs with selective NSAIDs (ie, celecoxib) associated with a lower risk for GI complications and a higher risk for CV complications compared to non-selective NSAIDs. Additionally, meloxicam was associated with a lower risk of ulcer complications compared to other non-selective NSAIDs *(Chou et al 2011).*

CLINICAL GUIDELINES

- **RA:** The American College of Rheumatology (ACR) guideline does not address the role of analgesics in management of RA. Treatment of RA is guided by a treat to target approach using DMARD therapy. Analgesics, including NSAIDs, have a limited role in most patients with active disease, but may be considered as a temporary adjunctive option (*Moreland et al 2020, Singh et al 2015*).
- **OA:** The ACR strongly recommends the use of oral NSAIDs as a class for the treatment of hand, hip, and knee OA. However, topical NSAIDs should be considered prior to use of oral NSAIDs for OA of the knee (strongly recommended) or hand (conditionally recommended); topical administration of NSAIDs for hip OA is unlikely to be of benefit. The guidance notes the relative differences between NSAIDs were not considered, but clinicians should consider that certain NSAIDs may have a more favorable adverse effect profile. Additional strongly or conditionally pharmacologic recommendations include IA glucocorticoid injections, acetaminophen, duloxetine, topical capsaicin, and tramadol *(Kolasinski et al 2020).*
  - Doses of oral NSAIDs should be as low as possible and continued for as short of time as possible.
- **Primary dysmenorrhea:** Based upon a Cochrane review of 73 randomized controlled trials, the American Academy of Family Physicians recommends oral NSAIDs as first-line treatment for primary dysmenorrhea. Specifically, guidelines support the use of celecoxib, ibuprofen, mefenamic acid, and naproxen. Choice of NSAID should be based on individual patient characteristics as no NSAID has been shown to be more effective than any other. Treatment initiation is recommended 1 to 2 days before expected onset of menses, with treatment duration of 2 to 3 days *(Osayande et al 2014).* Additionally, the American College of Obstetricians and Gynecologists also recommends that NSAIDs should be a first line treatment for management of primary dysmenorrhea in adolescents *(ACOG 2018).*
- **AS:** A joint guideline by the ACR, Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network strongly recommends treatment of active AS with oral NSAIDs. Additionally, a conditional recommendation was provided for continuous treatment with NSAIDs over on-demand treatment. As no formal comparative effectiveness studies of NSAIDs were available, the guideline recommended against designating any particular NSAID as the preferred treatment option. Instead, choice of NSAID should be determined by each patient's history, risk factors, and comorbidities *(Ward et al 2016, Ward et al 2019).*
- **JIA:** ACR recommendations for JIA include initiation of NSAID monotherapy in patients without prior treatment for a maximum of 1 month. The guideline specifically states that continuation of NSAID monotherapy for longer than 2 months in patients with continued disease activity is inappropriate. Both recommendations were based on expert opinion *(Ringold et al 2013).* Updated recommendations for certain populations with JIA are available and recommendations for NSAIDs are specific to each population *(Ringold et al 2019)*:
  - Updated recommendations for patients with JIA and polyarthritis include a conditional recommendation for adjunct therapy with NSAIDs, largely for symptom management, particularly during initiation or escalation of therapy with DMARDs or biologics. Initial therapy with a DMARD is strongly recommended over NSAID monotherapy.
  - For those with active sacroiliitis, treatment with a NSAID is strongly recommended for initial therapy, with addition of a TNF inhibitor for those with active disease despite NSAID treatment. Patients with active enthesitis should also be offered NSAID therapy initially, with TNF inhibitors, methotrexate, and sulfasalazine as add-on options for those without an adequate response.
- **Acute migraine:** The American Headache Society guidelines for acute treatment of migraine include various degrees of recommendations for use of oral NSAIDs depending on the specific agent. Aspirin, diclofenac, ibuprofen, and naproxen are recommended as having established efficacy. Additional NSAIDs including flurbiprofen and ketoprofen are recommended as probably effective, while celecoxib was deemed to have conflicting or inadequate evidence to support or refute use (*Marmura et al 2015).* For children and adolescents with migraine, ibuprofen (oral solution, 7.5 to 10 mg/kg), acetaminophen, and triptans (primarily adolescents) have supportive evidence for use in acute migraine to relieve pain *(Oskoui et al 2019).*
- **Gout:** Oral NSAIDs are recommended both by the ACR and the American College of Physicians as an appropriate treatment option for acute gout, though the ACP guidance recommends corticosteroids over NSAIDs in patients without contraindications due to their more favorable adverse effect profile. Neither guideline found clinically important differences between NSAIDs and did not recommend any specific NSAID over the others *(Khanna et al 2012, Qaseem et al 2017).*
  - The ACR also supports use of low-dose NSAID therapy as an appropriate first-line method of prophylaxis for acute gout attacks.
  - No consensus was reached on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

SAFETY SUMMARY

- **Boxed warnings:**
  - All oral NSAID products with the exception of Durlaza (aspirin ER) share the 2 boxed warnings below for CV and GI risk:
    - Serious CV thrombotic events: NSAIDs cause an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. NSAIDs are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
    - Serious GI bleeding, ulcerations and perforation: NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
  - Ketorolac carries additional boxed warnings for the following:
    - Renal risk: Ketorolac is contraindicated in patients with advanced renal function impairment and in patients at risk for renal failure due to volume depletion.
    - Risk of bleeding: Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and in those at high risk of bleeding. Ketorolac is contraindicated as a prophylactic analgesic before any major surgery.
    - Risk during labor and delivery: The use of ketorolac tromethamine in labor and delivery is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions.
    - Concomitant use with NSAIDs: Ketorolac is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related side effects.
    - Special populations: Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine.
- **Contraindications:**
  - Most oral NSAID products share a contraindication for use in the setting of CABG surgery, as well as in patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Additional contraindications specific to individual compounds are listed below.
  - Celebrex (celecoxib)
    - History of allergic-type reactions to sulfonamides
  - Fenoprofen (Profeno only):
    - History of significantly impaired renal function
  - Meloxicam (Qmiiz ODT only):
    - Patients with phenylketonuria
  - Ketorolac:
    - Active or history of peptic ulcer disease; recent or history of GI bleeding or perforation
    - Prophylactic analgesic before any major surgery
    - Advanced renal impairment or patients at risk for renal failure because of volume depletion
    - Labor and delivery
    - Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding
    - Patients currently receiving aspirin or NSAIDs
    - Concomitant use with probenecid or pentoxifylline.
- **Warnings and precautions:**
  - Most oral NSAID products share similar warnings and precautions for:
    - Increased risk of CV thrombotic events
    - New onset or worsening of hypertension
    - Increased risk of hospitalization due to heart failure and increased edema
    - Risk of GI effects including ulceration, bleeding, and perforation
    - Risk of renal injury and toxicity
    - Potential for skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
    - Risk of premature closure of the ductus arteriosus when used in late pregnancy
    - Borderline elevations of one or more liver tests

- Potential for anemia
- Risk of severe bronchospasm in patients with preexisting aspirin-sensitive asthma
- Risk of Reye's syndrome

○ Ketorolac:

- The total combined duration of use of ketorolac tromethamine tablets and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in pediatric patients.

- **Adverse events:**
  - Adverse events were similar among products and commonly included GI complaints (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, gastric/duodenal GI ulcers, and vomiting), abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Anaprox DS (naproxen sodium)	Tablets	Oral	Twice daily
Cambia (diclofenac potassium)	Powder for oral solution	Oral	Once as needed
Celebrex (celecoxib)	Capsules	Oral	Once to twice daily
Daypro (oxaprozin)	Tablets	Oral	Once daily
diclofenac	Capsules	Oral	Two to four times daily
diclofenac potassium	Tablets	Oral	Two to four times daily
diclofenac sodium DR	Tablets	Oral	Two to four times daily
diclofenac sodium ER	Tablets	Oral	Once daily
diflunisal	Tablets	Oral	Two to three times daily
Durlaza (aspirin ER)	Capsules	Oral	Once daily
EC-Naprosyn (naproxen DR)	Tablets	Oral	Twice daily
etodolac	Capsules	Oral	Two to four times daily
etodolac ER	Tablets	Oral	Once daily
Feldene (piroxicam)	Capsules	Oral	Once daily
flurbiprofen	Tablets	Oral	Two to four times daily
ibuprofen	Capsules, Suspension, Tablets, Chewable tablets	Oral	Three to six times daily
Indocin (indomethacin)	Capsules, Suspension	Oral	Two to four times daily
indomethacin ER	Capsules	Oral	Once to twice daily
ketoprofen	Capsules	Oral	Three to four times daily
ketoprofen ER	Capsules	Oral	Once daily
ketorolac	Tablets	Oral	Four to six times daily
Lodine (etodolac)	Tablets	Oral	Two to four times daily
Meclofen (meclofenamate)	Capsules	Oral	Three to four times daily
Mefenam (mefenamic acid)	Capsules	Oral	Four times daily
Mobic (meloxicam)	Tablets	Oral	Once daily
nabumetone	Tablets	Oral	Once to twice daily
Nalfon (fenoprofen)	Capsules, Tablets	Oral	Three to four times daily
Naprelan (naproxen sodium SR)	Tablets	Oral	Once daily
Naprosyn (naproxen)	Suspension, Tablets	Oral	Twice daily
Qmiiz ODT (meloxicam)	Orally disintegrating tablets	Oral	Once daily

Drug	Available Formulations	Route	Usual Recommended Frequency
Relafen DS (nabumetone)	Tablets	Oral	Once to twice daily
sulindac	Tablets	Oral	Twice daily
Tivorbex (indomethacin)	Capsules	Oral	Two to three times daily
tolmetin	Capsules, Tablets	Oral	Three times daily
Vivlodex (meloxicam)	Capsules	Oral	Once daily
Zipsor (diclofenac potassium)	Capsules	Oral	Four times daily
Zorvolex (diclofenac)	Capsules	Oral	Three times daily

See the current prescribing information for full details

CONCLUSION

- Oral NSAIDs are efficacious for the treatment of pain, RA, OA, primary dysmenorrhea, AS, acute migraine, and acute gout. Multiple systematic reviews and meta-analyses have shown that NSAIDs are superior to placebo for these indications. Furthermore, practice guidelines for most of these conditions recommend NSAIDs as a first-line treatment option.
- The totality of currently available evidence on relative efficacy between the available NSAIDs suggests that in general, there does not appear to be a significant difference in efficacy among the NSAIDs. Clinical practice guidelines for the aforementioned conditions support this finding and either recommend the use of NSAIDs as a class or recommend a list of NSAIDs for potential use without specifying a preference between listed agents.
- All NSAIDs carry some degree of risk for adverse events including CV thrombotic events and GI bleeding, ulceration, and perforation. Available evidence for the relative risk of these adverse events amongst NSAIDs is conflicting and inconclusive at this time. All reviewed NSAIDs with the exception of Durlaza (aspirin ER) carry the same boxed warnings for CV and GI risk. Contraindications, warnings/precautions, and adverse effects are similar among products.
- Differences between oral NSAIDs include FDA-labeled indications, available dosage formulations and strengths, and dosing frequency.

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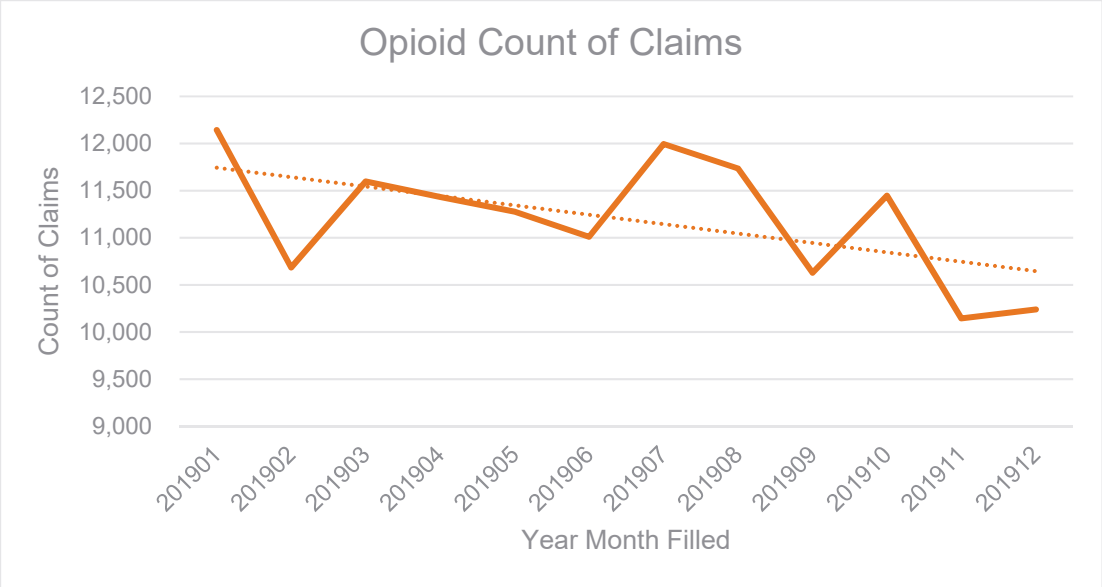
Publication Date: March 9, 2020

Board Requested Reports

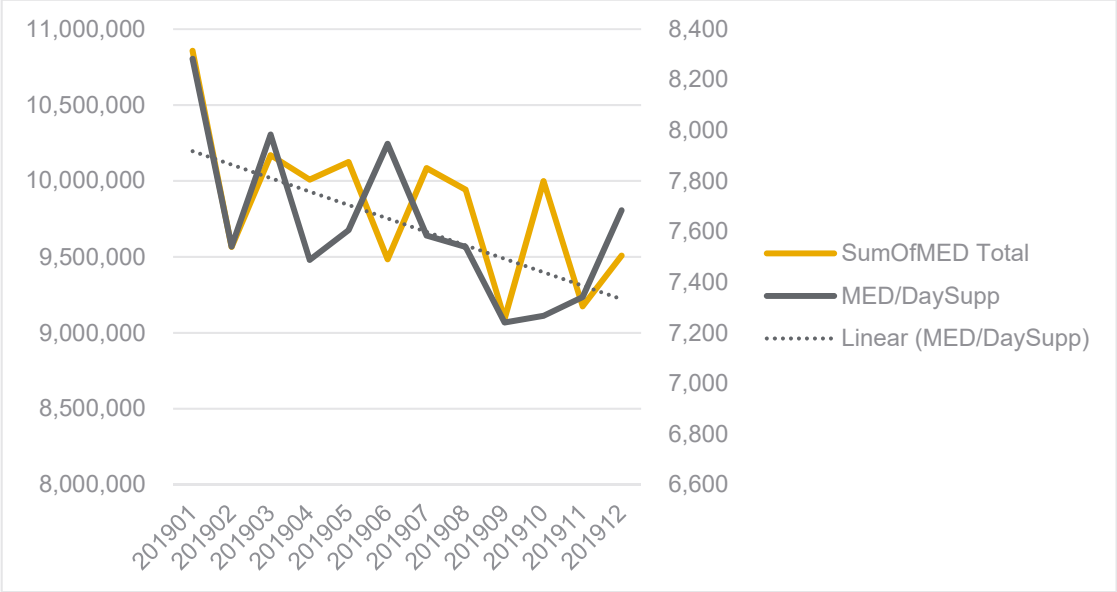
Nevada Medicaid

Opioid Utilization Summary
Fee for Service
January 1, 2019 - December 31, 2019

Date Filled	Member ID	RxCLAIM Number	Total Days Supply	Total Quantity
201901	8,511	12,143	221,369	746,632
201902	7,771	10,685	197,232	658,901
201903	8,155	11,598	209,717	695,342
201904	8,095	11,433	209,383	697,257
201905	7,949	11,277	211,213	710,832
201906	7,894	11,011	198,680	656,070
201907	8,242	11,995	212,343	699,821
201908	8,133	11,736	211,887	693,706
201909	7,759	10,628	195,916	638,085
201910	8,146	11,447	213,341	702,686
201911	7,553	10,144	194,581	643,979
201912	7,564	10,239	199,485	662,763



Date Filled	SumOfMED Total	MED/DaySupp
201901	10,857,253	8,283
201902	9,565,922	7,541
201903	10,170,046	7,984
201904	10,008,606	7,488
201905	10,125,218	7,605
201906	9,484,260	7,947
201907	10,085,288	7,584
201908	9,942,722	7,539
201909	9,092,428	7,241
201910	9,999,040	7,267
201911	9,174,313	7,341
201912	9,508,778	7,684



Opioid Utilization by Prescriber - Top 10

Fee for Service Medicaid

Quarter 3, 2019 and Quarter 4, 2019

Q3 2019 By MED/Day Supply

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Total MED	MED/DS
AL	MD - Internal M	Reno	1	1	2	6	4,320	2,160
AE	MD - Oncology	Las Vegas	1	1	30	240	10,800	360
X	MD - Oncology	Las Vegas	1	2	60	180	18,000	300
U	NP	Henderson	2	2	60	210	14,400	240
W	DPM	Las Vegas	2	2	60	120	14,400	240
AA	MD - Oncology	Henderson	3	8	230	1,920	54,000	235
V	MD - Internal M	Las Vegas	3	5	127	741	29,805	235
AH	NP	Las Vegas	2	2	60	450	13,950	233
AK	NP	Salt Lake City	2	4	120	515	25,875	216
AD	MD - Internal M	Las Vegas	4	10	290	1,620	60,750	209

Q3 2019 By Total MED

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Total MED	MED/DS
A	MD - Anesthesi	Reno	180	459	13,384	51,603	750,896	56
B	PA - No Special	Las Vegas	125	228	6,450	21,459	564,583	88
C	PA - Pain Mana	Las Vegas	107	266	7,539	27,274	507,263	67
D	MD - Pain Mana	Las Vegas	133	239	7,128	21,015	462,485	65
E	PA - No Special	Las Vegas	105	177	5,162	16,811	397,290	77
F	PA - Orthopedi	Las Vegas	159	295	8,550	28,307	389,602	46
G	PA - No Special	Las Vegas	118	300	8,774	28,551	350,023	40
H	PA - No Special	Las Vegas	110	182	5,173	17,273	335,483	65
I	PA - No Special	Las Vegas	155	277	8,200	25,392	333,475	41
J	PA - Pain Mana	Las Vegas	118	210	6,071	23,930	326,776	54

Q4 2019 By MED/Day Supply

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Total MED	MED/DS
AA	MD - Oncology	Henderson	5	7	162	1,272	43,770	270
Y	MD - Oncology	Las Vegas	1	4	80	480	21,600	270
AG	MD - Internal M	Las Vegas	3	6	180	975	42,188	234
V	MD - Internal M	Las Vegas	3	5	127	771	29,655	234
Z	MD - Oncology	Reno	6	11	307	1,694	69,740	227
AC	DO - Internal M	Las Vegas	3	7	194	1,136	40,780	210
AB	NP	Las Vegas	10	16	397	1,429	82,005	207
AJ	MD - Pain Mana	Las Vegas	10	27	767	4,764	151,830	198
AI	MD - Orthoped	Las Vegas	1	1	14	180	2,700	193
AF	MD - Oncology	Las Vegas	14	36	1,086	4,334	203,730	188

Q4 2019 By Total MED

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Total MED	MED/DS
A	MD - Anesthesi	Reno	177	451	12,951	52,401	674,156	52
P	MD - Pain Mana	Las Vegas	172	412	11,167	36,506	664,400	59
Q	MD - Pain Mana	Las Vegas	283	435	12,433	37,789	488,304	39
B	PA - No Special	Las Vegas	100	181	4,956	16,692	461,140	93
T	NP - Pain Mana	Las Vegas	126	260	7,735	22,779	451,493	58
R	MD - Internal M	Las Vegas	115	219	5,366	17,149	419,620	78
F	PA - Orthopedi	Las Vegas	174	332	9,591	30,403	419,359	44
G	PA - No Special	Las Vegas	118	303	8,998	29,957	386,323	43
C	PA - Pain Mana	Las Vegas	84	218	6,036	21,434	381,600	63
E	PA - No Special	Las Vegas	61	136	4,000	13,615	319,350	80

Opioid Utilization by Member - Top 10

Fee for Service Medicaid

Quarter 4, 2019

Member ID Encrypted	Count of Claims	Days Supply	Total Qty	MED Total
77771952964	6	180	750	67,500
44448546720	8	240	1,680	63,000
22222296971	8	165	612	58,590
33330458115	6	180	1,080	57,600
44446597311	6	180	585	56,700
40006322223	6	180	405	48,600
00009186655	9	270	600	48,600
76050522223	6	180	720	45,900
49044066667	6	168	924	45,360
66667788323	9	270	990	44,550

Member ID Encrypted	GPI Name	Column1	Column2	MED Value per Unit	Count of Claims	Days Supply	Total Qty	MED Total
00009186655	FENTANYL TD PAT 72H 100MCG/HR			720	3	90	30	21,600
00009186655	FENTANYL TD PAT 72H 50MCG/HR			360	3	90	30	10,800
00009186655	OXYCODONE HCL TAB 20 MG			30	3	90	540	16,200
22222296971	FENTANYL TD PAT 72H 100MCG/HR			720	1	6	2	1,440
22222296971	FENTANYL TD PAT 72H 75MCG/HR			540	3	90	60	32,400
22222296971	OXYCODONE HCL TAB 30 MG			45	4	69	550	24,750
33330458115	MORPHINE SULF TAB CR 100 MG			100	3	90	360	36,000
33330458115	OXYCODONE HCL TAB 20 MG			30	3	90	720	21,600
40006322223	FENTANYL TD PAT 72H 100MCG/HR			720	3	90	45	32,400
40006322223	OXYCODONE HCL TAB 30 MG			45	3	90	360	16,200
44446597311	FENTANYL TD PAT 72H 100MCG/HR			720	3	90	45	32,400
44446597311	OXYCODONE HCL TAB 30 MG			45	3	90	540	24,300
44448546720	HYDROCODONE-APAP TAB 10-325 MG			10	4	120	360	3,600
44448546720	OXYCODONE HCL TAB 30 MG			45	4	120	1,320	59,400
49044066667	MORPHINE SULF TAB CR 60 MG			60	3	84	252	15,120
49044066667	OXYCODONE HCL TAB 30 MG			45	3	84	672	30,240
66667788323	MORPHINE SULF TAB CR 30 MG			30	3	90	270	8,100
66667788323	MORPHINE SULF TAB CR 60 MG			60	3	90	270	16,200
66667788323	OXYCODONE HCL TAB 30 MG			45	3	90	450	20,250
76050522223	OXYCOD TAB ER12H DETER 80MG			120	3	90	180	21,600
76050522223	OXYCODONE HCL TAB 30 MG			45	3	90	540	24,300
77771952964	FENTANYL TD PAT 72H 100MCG/HR			720	2	60	60	43,200
77771952964	METHADONE HCL TAB 10 MG				1	30	150	-
77771952964	OXYCODONE HCL TAB 30 MG			45	3	90	540	24,300

Methadone Utilization by Service Location

Fee for Service Medicaid

January 1, 2019 - December 31, 2019

Row Labels		Count of Members	Count of Claims	Days Supply	Total Qty
Chain LTC		**12**	**121**	**1,703**	**12,542**
METHADONE	SOL 5MG/5ML	1	15	286	4,335
METHADONE	TAB 10MG	6	56	901	5,405
METHADONE	TAB 5MG	5	50	516	2,802
Chain Retail		**233**	**1,116**	**32,564**	**123,867**
METHADONE	SOL 5MG/5ML	3	3	52	137
METHADONE	TAB 10MG	195	972	28,438	114,147
METHADONE	TAB 5MG	35	141	4,074	9,583
Hospice		**2**	**5**	**5**	**5**
METHADONE	CON 10MG/ML	1	3	3	3
METHADONE	SOL 5MG/5ML	1	2	2	2
Hospital		**71**	**133**	**436**	**2,543**
DOLOPHINE	TAB 10MG	4	8	8	9
METHADONE	CON 10MG/ML	3	5	34	38
METHADONE	SOL 10MG/5ML	2	2	2	75
METHADONE	SOL 5MG/5ML	3	5	105	1,455
METHADONE	TAB 10MG	48	99	273	944
METHADONE	TAB 5MG	7	9	9	12
METHADOSE	TAB 40MG	4	5	5	11
Ind Retail		**53**	**261**	**7,590**	**33,994**
METHADONE	TAB 10MG	45	222	6,504	31,719
METHADONE	TAB 5MG	8	39	1,086	2,275
Grand Total		**371**	**1,636**	**42,298**	**172,951**

Drug Label Name		Count of Members	Count of Claims	Days Supply	Total Qty
DOLOPHINE	TAB 10MG	4	8	8	9
METHADONE	TAB 5MG	41	239	5,685	14,672
METHADONE	SOL 10MG/5ML	2	2	2	75
METHADONE	CON 10MG/ML	4	8	37	41
METHADONE	TAB 10MG	181	1,349	36,116	152,215
METHADOSE	TAB 40MG	4	5	5	11
METHADONE	SOL 5MG/5ML	8	25	445	5,929

Antibiotic Utilization

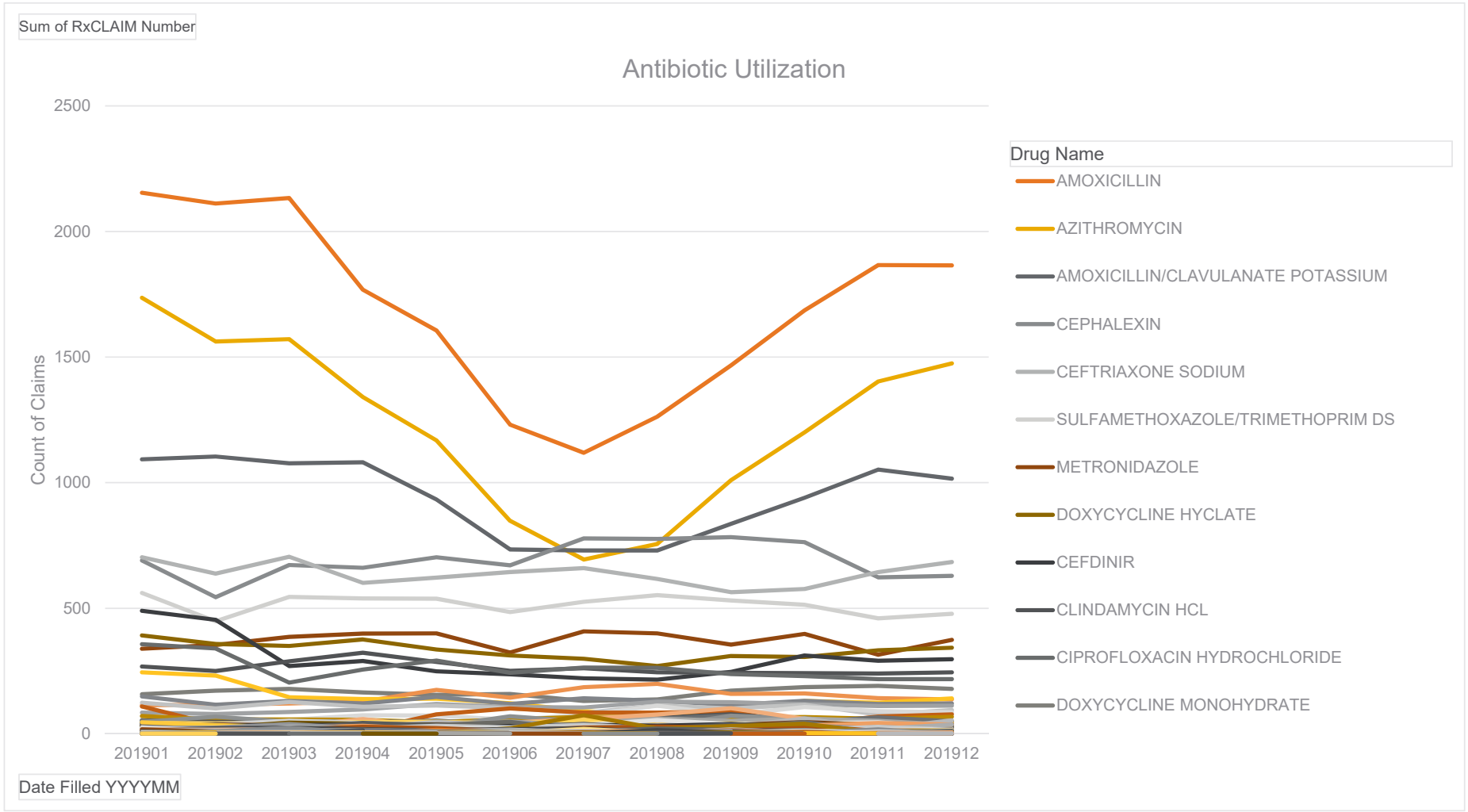
Fee for Service Medicaid

January 1, 2019 - December 31, 2019

Drug Name	Count of Me	Count of Claims	Day Supply	Total Qty
AMOXICILLIN	15,429	20,269	183,354	1,843,948
AZITHROMYCIN	11,286	14,764	69,203	134,551
AMOXICILLIN/CLAVULANATE POTASSIUM	9,111	11,326	100,746	502,526
CEPHALEXIN	6,433	8,293	66,874	404,189
CEFTRIAXONE SODIUM	5,345	7,659	8,146	193,335
SULFAMETHOXAZOLE/TRIMETHOPRIM DS	4,491	6,177	61,046	109,687
METRONIDAZOLE	3,285	4,452	28,169	163,638
DOXYCYCLINE HYCLATE	2,808	3,985	51,531	91,790
CEFDINIR	3,006	3,574	31,485	168,340
CLINDAMYCIN HCL	2,553	3,143	25,474	88,846
CIPROFLOXACIN HYDROCHLORIDE	2,400	3,123	23,511	45,762
DOXYCYCLINE MONOHYDRATE	1,365	1,984	31,683	56,159
CEFAZOLIN SODIUM	1,423	1,783	2,046	20,272
LEVOFLOXACIN	1,328	1,685	12,190	13,426
PENICILLIN V POTASSIUM	1,133	1,544	17,931	91,070
VANCOMYCIN HYDROCHLORIDE	809	1,274	3,900	117,506
SULFAMETHOXAZOLE/TRIMETHOPRIM	729	1,261	21,747	136,527
CLINDAMYCIN HYDROCHLORIDE	817	935	8,253	36,628
DAPTOMYCIN	72	836	1,692	2,205
ERYTHROMYCIN ETHYLSUCCINATE	81	742	9,880	112,754
PIPERACILLIN/TAZOBACTAM	459	609	724	1,111
CEFEPIME	295	603	1,294	43,204
ERTAPENEM SODIUM	51	572	740	741
CEFTRIAXONE IN ISO-OSMOTIC DEXTROSE	415	546	603	31,700
VANCOMYCIN HCL	98	545	564	145,319
MINOCYCLINE HYDROCHLORIDE	203	506	15,387	25,017
XIFAXAN	107	454	11,935	24,283
LINEZOLID	208	453	3,013	174,321
CLARITHROMYCIN	371	436	5,283	13,435
CEFTRIAXONE/DEXTROSE	251	416	416	1,479
CLINDAMYCIN PALMITATE HCL	340	408	3,683	114,821
CEFUROXIME AXETIL	341	405	3,277	6,601
CEFAZOLIN SODIUM/DEXTROSE	359	402	439	5,085
TOBRAMYCIN	108	365	11,111	91,430
ZOSYN	233	350	442	25,954
INVANZ	33	318	318	328
AMPICILLIN-SULBACTAM	235	303	332	515
LEVOFLOXACIN IN D5W	230	290	334	42,700
BICILLIN L-A	242	287	620	883
MEROPENEM	81	276	477	14,333
CIPROFLOXACIN I.V.-IN D5W	191	276	299	77,800
SULFATRIM PEDIATRIC	167	244	3,258	38,727
CLEOCIN PHOSPHATE	195	243	243	10,414
CUBICIN	13	231	231	235
GENTAMICIN SULFATE	137	191	460	1,369
PIPERACILLIN SODIUM/TAZOBACTAM SODIUM	118	148	236	510
ZITHROMAX	125	138	138	315
CLEOCIN IN D5W	114	128	128	17,750
VANCOMYCIN HYDROCHLORIDE/DEXTROSE	39	114	337	128,650
ERTAPENEM	34	110	593	594
CLINDAMYCIN/SODIUM CHLORIDE	74	109	115	9,600
CEFPODOXIME PROXETIL	86	108	944	7,447
MINOCYCLINE HCL	44	106	3,524	5,139
CEFAZOLIN	73	105	116	18,800
DAPSONE	14	105	1,913	2,168
ERYTHROMYCIN BASE	55	96	2,189	5,535
TETRACYCLINE HYDROCHLORIDE	64	94	1,795	4,570
COLISTIMETHATE SODIUM	25	93	533	887

Drug Name	Count of Me	Count of Claims	Day Supply	Total Qty
DOXY 100	67	88	88	149
FIRVANQ	57	87	990	18,153
MOXIFLOXACIN HYDROCHLORIDE	67	85	473	3,463
CAYSTON	21	82	2,800	6,888
CEFOXITIN SODIUM	62	80	80	310
BACITRACIN	72	75	75	162
AMPICILLIN	59	69	569	1,997
PENTAM 300	13	64	122	66
CLINDAMYCIN PHOSPHATE	54	63	63	348
NEOMYCIN SULFATE	27	57	629	1,491
UNASYN	41	54	54	57
TOBRAMYCIN SULFATE	30	54	154	1,261
CEFPROZIL	43	52	558	6,245
TRIMETHOPRIM	18	51	1,652	2,852
CLINDAMYCIN PHOSPHATE/DEXTROSE	38	50	61	5,550
CIPRO	25	46	404	4,825
ZITHROMAX Z-PAK	38	42	42	42
CIPROFLOXACIN HCL	34	42	708	986
ZYVOX	11	42	42	19,815
ATOVAQUONE	19	39	990	9,810
DICLOXACILLIN SODIUM	36	39	373	1,507
AZTREONAM	33	38	62	473
TAZICEF	12	31	31	40
AMOXICILLIN/CLAVULANATE POTASSIUM ER	22	29	236	702
CUBICIN RF	15	27	27	45
DOXYCYCLINE HYCLATE DR	25	27	384	632
TINIDAZOLE	23	25	75	236
BETHKIS	8	24	924	5,376
BAXDELA	15	23	394	758
CEFTAZIDIME	4	22	22	48
DOXYCYCLINE	6	21	298	9,000
OXACILLIN SODIUM	6	19	68	15,416
TOBI PODHALER	6	18	700	4,032
CEFOTETAN/DEXTROSE	15	18	18	1,000
ERYPED 200	8	18	449	6,002
AMPICILLIN SODIUM	17	18	25	172
MEROPENEM/SODIUM CHLORIDE	10	17	17	1,650
AVYCAZ	4	17	44	106
AMIKACIN SULFATE	9	17	168	422
DEMECLOCYCLINE HCL	3	16	364	792
CEFOTETAN	12	15	15	162
TEFLARO	12	14	32	53
CEFIXIME	4	13	309	1,111
CLARITHROMYCIN ER	12	13	114	228
CEFADROXIL	10	12	110	224
PENICILLIN G POTASSIUM	3	12	12	43
MERREM	8	11	11	13
MINOCYCLINE HYDROCHLORIDE ER	6	11	390	390
BICILLIN C-R	11	11	11	62
AUGMENTIN	11	11	92	1,705
CEFACLOR	9	11	195	319
DIFICID	8	9	63	125
PENICILLIN G POTASSIUM IN ISO-OSMOTIC DEXTROSE	3	9	51	15,950
MAXIPIME	7	9	9	700
PFIZERPEN	5	8	8	2
GENTAMICIN SULFATE/0.9% SODIUM CHLORIDE	7	8	8	850
SULFADIAZINE	1	8	240	1,920
ISOTONIC GENTAMICIN	8	8	8	1,000
ORBACTIV	3	8	66	45
CEFUROXIME SODIUM	5	7	7	13
DALVANCE	6	6	6	18
ERYTHROMYCIN	5	6	113	327
AZACTAM	4	6	6	6

Drug Name	Count of Me	Count of Claims	Day Supply	Total Qty
VANCOMYCIN	1	5	9	3,450
TIGECYCLINE	1	5	18	36
CEFEPIME/DEXTROSE	1	4	15	30
ZERBAXA	2	4	18	54
ERYTHROMYCIN DR	3	4	180	270
SIVEXTRO	3	4	24	24
ERY-TAB	3	4	33	94
XERAVA	1	4	23	92
XIMINO	1	4	120	120
CEFTAZIDIME/DEXTROSE	3	4	4	5
E.E.S. GRANULES	3	4	71	1,101
STREPTOMYCIN SULFATE	1	4	4	2
VIBRAMYCIN	3	3	42	735
BACTRIM DS	3	3	3	3
CLINDAMYCIN PHOSPHATE IN D5W	3	3	3	150
FLAGYL	2	2	2	2
CLEOCIN PEDIATRIC GRANULES	2	2	2	10
UNASYN BULK PACK	1	2	2	0
ERYTHROCIN LACTOBIONATE	1	2	2	2
LINCOMYCIN HCL	2	2	2	1
SUPRAX	1	2	20	20
PENTAMIDINE ISETHIONATE	1	2	60	2
ARIKAYCE	1	1	28	235
PRIMAXIN IV	1	1	1	2
GENTAMICIN SULFATE PEDIATRIC	1	1	1	8
LINCOCIN	1	1	1	2
SOLODYN	1	1	30	30
ERYTHROCIN STEARATE	1	1	30	60
MOXIFLOXACIN HYDROCHLORIDE/SODIUM HYDROCHLORIDE	1	1	1	250
CEFOTAN	1	1	1	1
VANCOCIN	1	1	1	1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Count of Claims
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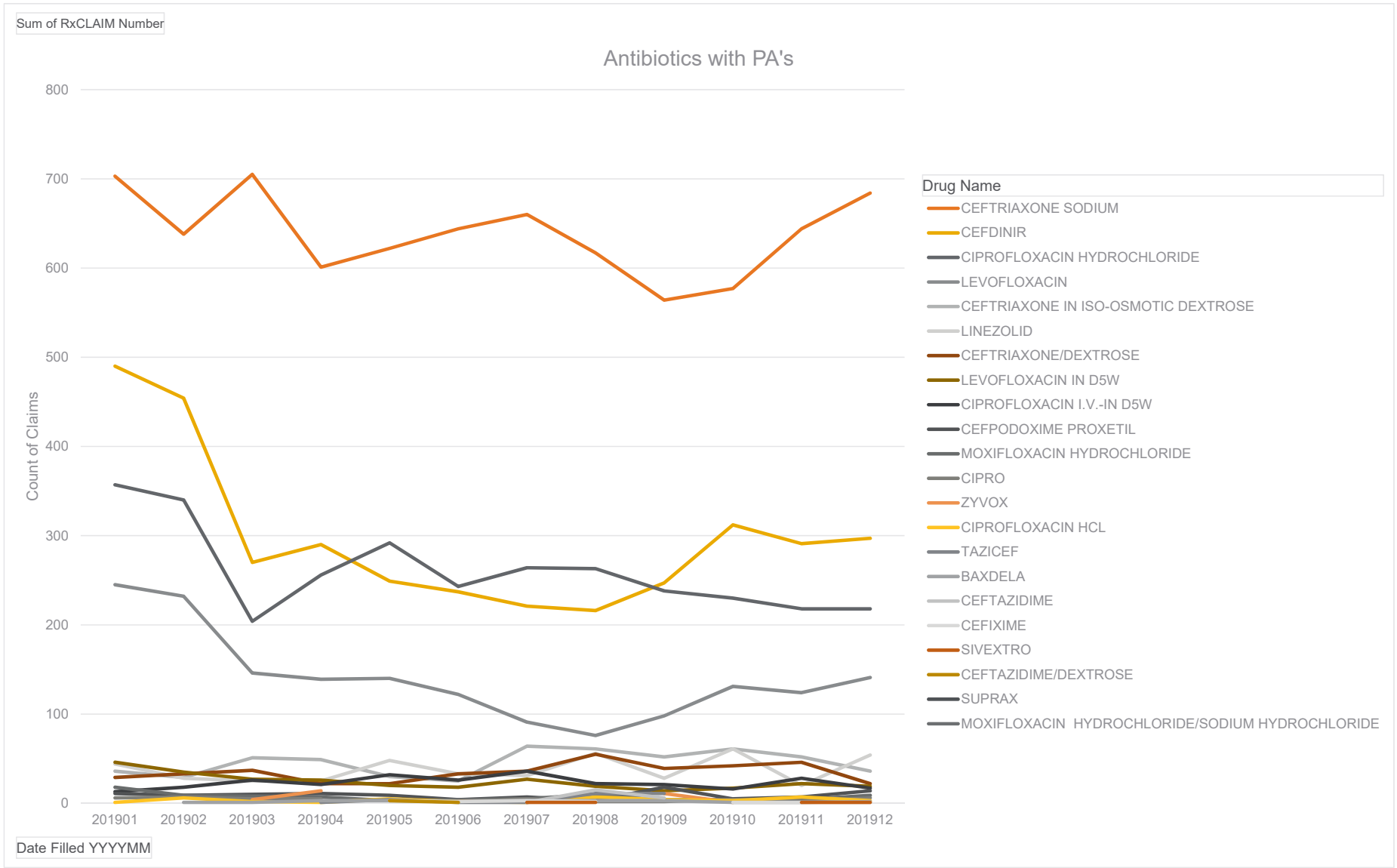
201902
201903
201904
201905
201906
201907
201908
201909
201910
201911
201912
Date Filled YYYYMM
Drug Name
AMOXICILLIN
AZITHROMYCIN
AMOXICILLIN/CLAVULANATE POTASSIUM
CEPHALEXIN
CEFTRIAXONE SODIUM
SULFAMETHOXAZOLE/TRIMETHOPRIM DS
METRONIDAZOLE
DOXYCYCLINE HYCLATE
CEFDINIR
CLINDAMYCIN HCL
CIPROFLOXACIN HYDROCHLORIDE
DOXYCYCLINE MONOHYDRATE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Antibiotics with PA's
800
700
600
500
400
300
200
100
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Count of Claims
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201902
201903
201904
201905
201906
201907
201908
201909
201910
201911
201912
Date Filled YYYYMM
Drug Name
CEFTRIAXONE SODIUM
CEFDINIR
CIPROFLOXACIN HYDROCHLORIDE
LEVOFLOXACIN
CEFTRIAXONE IN ISO-OSMOTIC DEXTROSE
LINEZOLID
CEFTRIAXONE/DEXTROSE
LEVOFLOXACIN IN D5W
CIPROFLOXACIN I.V.-IN D5W
CEFPODOXIME PROXETIL
MOXIFLOXACIN HYDROCHLORIDE
CIPRO
ZYVOX
CIPROFLOXACIN HCL
TAZICEF
BAXDELA
CEFTAZIDIME
CEFIXIME
SIVEXTRO
CEFTAZIDIME/DEXTROSE
SUPRAX
MOXIFLOXACIN HYDROCHLORIDE/SODIUM HYDROCHLORIDE

Standard DUR Reports

Nevada Medicaid

Top 10 Therapeutic Classes

Fee for Service

Quarter 3, 2019 and Quarter 4, 2019

Top 10 Drug Classes by Paid Amount - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTIHEMOPHILIC PRODUCTS**	122	$ 13,142,137
ANTIRETROVIRALS**	2,084	$ 3,657,346
INSULIN**	4,490	$ 3,117,897
SYMPATHOMIMETICS**	19,159	$ 2,695,883
ANTICONVULSANTS - MISC.**	26,148	$ 2,447,071
BENZISOXAZOLES**	5,524	$ 2,362,985
ANTIPSYCHOTICS - MISC.**	2,783	$ 2,240,605
QUINOLINONE DERIVATIVES**	4,969	$ 1,823,960
ANTINEOPLASTIC ENZYME INHIBITORS**	154	$ 1,658,912
LOCAL ANESTHETICS - TOPICAL**	1,633	$ 1,650,028

Top 10 Drug Classes by Paid Amount - Previous Quarter

Drug Class Name	RxCLAIM Number	Response Due Amount
ANTIHEMOPHILIC PRODUCTS**	112	$ 14,161,462
ANTIRETROVIRALS**	1,715	$ 3,630,727
INSULIN**	4,581	$ 3,291,499
SYMPATHOMIMETICS**	17,998	$ 2,687,346
ANTICONVULSANTS - MISC.**	26,257	$ 2,664,244
BENZISOXAZOLES**	5,657	$ 2,391,336
ANTIPSYCHOTICS - MISC.**	2,800	$ 2,183,592
QUINOLINONE DERIVATIVES**	4,823	$ 1,763,706
ANTINEOPLASTIC ENZYME INHIBITORS**	155	$ 1,762,465
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES**	263	$ 1,583,220

Top 10 Drug Classes by Claim Count - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,148	$ 2,447,071
SYMPATHOMIMETICS**	19,159	$ 2,695,883
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,907	$ 202,410
OPIOID COMBINATIONS**	15,188	$ 415,407
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	14,512	$ 308,642
CENTRAL MUSCLE RELAXANTS**	12,345	$ 212,679
HMG COA REDUCTASE INHIBITORS**	10,408	$ 337,723
OPIOID AGONISTS**	9,944	$ 587,258
DIBENZAPINES**	9,443	$ 372,070
ANTIANXIETY AGENTS - MISC.**	8,014	$ 124,972

Top 10 Drug Classes by Claim Count - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,257	$ 2,664,244
SYMPATHOMIMETICS**	17,998	$ 2,687,346
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,934	$ 207,464
OPIOID COMBINATIONS**	15,212	$ 440,104
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	14,258	$ 347,636
CENTRAL MUSCLE RELAXANTS**	12,552	$ 223,339
HMG COA REDUCTASE INHIBITORS**	10,450	$ 338,271
OPIOID AGONISTS**	10,099	$ 640,496
DIBENZAPINES**	9,649	$ 378,382
BENZODIAZEPINES**	8,326	$ 103,423

RxTrack®

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

From 10/1/19 Through 12/31/19

Mar 20, 2020
1:43:03 PM

Claims Summary:

RxCLAIM Status	Total Rxs with cDUR(s)	% Total Rxs with cDUR(s)	Total Rxs with No cDURs	% Total Rxs with No cDURs	Total Rxs	% Total Rxs	Total Plan Paid	Total Member Paid
Paid	165,115	63.70%	96,070	46.23%	261,185	55.93%	$37,412,462.30	$0.00
Rejected	69,272	26.72%	96,887	46.62%	166,159	35.58%		
Reversed	24,826	9.58%	14,855	7.15%	39,681	8.50%		
Totals	**259,213**	**100.00%**	**207,812**	**100.00%**	**467,025**	**100.00%**		

cDUR Information Summary Table:

	Total cDURs			cDURs on Paid Rxs			cDURs on Rejected Rxs			cDURs on Reversed Rxs		
cDUR Type	Total cDUR Triggered Events	Count	% of All cDURs	Count	% of cDUR Type	% Total cDURs	Count	% of cDUR Type	% Total cDURs	Count	% of cDUR Type	% Total cDURs
Duplicate Rx (DUPRX)	70,734	67,889	26.19%	17,609	25.94%	10.66%	45,048	66.36%	65.03%	5,232	7.71%	21.07%
Drug-Drug Interaction (DDI-DTMS)	122,498	46,752	18.04%	33,684	72.05%	20.40%	10,094	21.59%	14.57%	2,974	6.36%	11.98%
Duplicate Therapy (DUPTHER)	146,105	58,562	22.59%	39,397	67.27%	23.86%	13,777	23.53%	19.89%	5,388	9.20%	21.70%
Drug Regimen Compliance (COMPLIAN)	42,085	38,755	14.95%	32,673	84.31%	19.79%	0	0.0%	0.0%	6,082	15.69%	24.50%
Dosing/Duration (DOSECHEK)	67,929	47,187	18.20%	41,706	88.38%	25.26%	353	0.75%	0.51%	5,128	10.87%	20.66%
Drug Age Caution (DRUG_AGE)	70	68	0.03%	46	67.65%	0.03%	0	0.0%	0.0%	22	32.35%	0.09%
Total All cDURs	**449,421**	**259,213**	**100.00%**	**165,115**	**63.70%**	**100.00%**	**69,272**	**26.72%**	**100.00%**	**24,826**	**9.58%**	**100.00%**

RXT6050D - Summarized DUR Activity Report

From 10/1/19 Through 12/31/19

* cDUR Information Summary results are sorted by Total cDUR count in descending order
* Some RxClaims could have multiple cDUR edit types
* The Count and % of cDUR Type for Paid, Rejected and Reversed Rxs are based on cDUR Type totals for each row

DUR Service	Top Drug Drug Interaction	GPI 4	GPI 4 Description	GPI 4/ Therapy / Reason	GPI 04 Description	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per RX	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount	Top PPS CODE USED #1	Top PPS CODE USED #2	Top PPS CODE USED #3
Dosing/Duration (DOSECHEK)	CYCLOBENZAPRINE HYDROCHLORIDE	7510	NA	MAX DAYS THERAPY = 21	CENTRAL MUSCLE RELAXANTS**	Message	2,074	$24,919.63	$9.46	$0.00	32.4	68.4	0	167	$1,597.59			
Dosing/Duration (DOSECHEK)	ONDANSETRON ODT	5025	NA	GERIATRIC MIN DLY = 2.00UN	5-HT3 RECEPTOR ANTAGONISTS**	Message	1,003	$494.52	$0.40	$0.00	1.6	1.4	0	16	$9.52			
Dosing/Duration (DOSECHEK)	FAMOTIDINE	4920	NA	GERIATRIC MIN DLY = 4.00UN	H-2 ANTAGONISTS**	Message	711	$708.47	$0.82	$0.00	1.0	2.0	0	20	$18.95			
Dosing/Duration (DOSECHEK)	ATORVASTATIN CALCIUM	3940	NA	MIN. DAYS THERAPY = 7	HMG COA REDUCTASE INHIBITORS**	Message	581	$167.59	$0.21	$0.00	1.0	1.3	0	42	$5.86			
Dosing/Duration (DOSECHEK)	HEPARIN SODIUM	8310	NA	GERIATRIC MIN DLY = 4.00UN	HEPARINS AND HEPARINOID-LIKE AGENTS**	Message	571	$2,210.65	$2.61	$0.00	1.1	1.7	0	33	$82.12			
Dosing/Duration (DOSECHEK)	POTASSIUM CHLORIDE ER	7970	NA	ADULT MIN DLY = 2.00 UN	POTASSIUM**	Message	502	$9,898.45	$15.85	$0.00	42.2	41.6	0	63	$973.18			
Dosing/Duration (DOSECHEK)	AMLODIPINE BESYLATE	3400	NA	MIN. DAYS THERAPY = 7	CALCIUM CHANNEL BLOCKERS**	Message	466	$137.58	$0.20	$0.00	1.0	1.2	0	17	$10.53			
Dosing/Duration (DOSECHEK)	PANTOPRAZOLE SODIUM	4927	NA	MIN. DAYS THERAPY = 7	PROTON PUMP INHIBITORS**	Message	437	$151.63	$0.30	$0.00	1.1	1.1	0	17	$2.11			
Dosing/Duration (DOSECHEK)	CETIRIZINE HYDROCHLORIDE	4155	NA	GERIATRIC MAX DLY = .50UN	ANTIHISTAMINES - NON-SEDATING**	Message	429	$4,894.11	$10.02	$0.00	38.7	38.7	0	27	$235.03			
Dosing/Duration (DOSECHEK)	LISINOPRIL	3610	NA	MIN. DAYS THERAPY = 7	ACE INHIBITORS**	Message	412	$127.24	$0.24	$0.00	1.1	1.3	0	28	$11.28			
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/DEXTROMETHORPHAN	4399	NA	AGE LESS THAN 4	COUGH/COLD/ALLERGY COMBINATIONS**	Message	25	$473.12	$12.02	$0.00	10.8	113.8	0	12	$149.57			
Drug Age Caution (DRUG_AGE)	NITROFURANTOIN	5300	NA	AGE LESS THAN 4	URINARY ANTI-INFECTIVES**	Message	7	$6,361.00	$391.74	$0.00	23.4	179.4	0	9	$3,618.82			
Drug Age Caution (DRUG_AGE)	PROMETHAZINE HCL PLAIN	4140	NA	AGE LESS THAN 4	ANTIHISTAMINES - PHENOTHIAZINES**	Message	5	$43.99	$7.31	$0.00	9.6	94.6	0	1	$7.42			
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/CODEINE	4399	NA	AGE LESS THAN 10	COUGH/COLD/ALLERGY COMBINATIONS**	Message	3	$32.46	$10.82	$0.00	6.7	120.0	0	0				
Drug Age Caution (DRUG_AGE)	CARBINOXAMINE MALEATE	4120	NA	AGE LESS THAN 4	ANTIHISTAMINES - ETHANOLAMINES**	Message	2	$42.90	$21.45	$0.00	14.0	118.0	0	0				
Drug Age Caution (DRUG_AGE)	ACETAMINOPHEN/CODEINE	6599	NA	AGE LESS THAN 10	OPIOID COMBINATIONS**	Message	2	$9.05	$4.52	$0.00	3.0	56.5	0	0				
Drug Age Caution (DRUG_AGE)	ACETAMINOPHEN/CODEINE	6599	NA	AGE LESS THAN 4	OPIOID COMBINATIONS**	Message	1	$4.00	$4.00	$0.00	3.0	20.0	0	0				
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/CODEINE	4399	NA	AGE LESS THAN 4	COUGH/COLD/ALLERGY COMBINATIONS**	Message	1	$10.82	$10.82	$0.00	10.0	120.0	0	0				
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7260	NA	7 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	51	$906.66	$13.77	$0.00	28.5	92.9	0	12	$189.46			
Drug Regimen Compliance (COMPLIAN)	ATORVASTATIN CALCIUM	3940	NA	7 DAYS LATE REFILLING	HMG COA REDUCTASE INHIBITORS**	Message	47	$645.09	$10.01	$0.00	30.5	31.2	0	10	$119.61			
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7260	NA	8 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	45	$719.89	$13.23	$0.00	29.9	97.0	0	5	$88.52			
Drug Regimen Compliance (COMPLIAN)	ATORVASTATIN CALCIUM	3940	NA	8 DAYS LATE REFILLING	HMG COA REDUCTASE INHIBITORS**	Message	43	$554.63	$11.40	$0.00	29.2	30.6	0	2	$24.32			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	7 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	36	$5,163.90	$90.95	$0.00	23.7	7.3	0	16	$1,463.72			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	9 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	36	$4,457.50	$97.33	$0.00	24.5	7.6	0	11	$953.70			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	12 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	36	$4,375.98	$88.69	$0.00	21.4	6.9	0	11	$1,183.26			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	10 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	35	$4,718.32	$97.94	$0.00	22.7	7.8	0	13	$1,203.62			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	8 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	34	$4,482.51	$94.09	$0.00	24.3	7.7	0	13	$1,283.34			
Drug Regimen Compliance (COMPLIAN)	MONTELUKAST SODIUM	4450	NA	8 DAYS LATE REFILLING	LEUKOTRIENE MODULATORS**	Message	33	$617.55	$12.26	$0.00	30.0	30.0	0	10	$185.50			
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	5710	NA	HYDROCO/APAP TAB 10-325MG	BENZODIAZEPINES**	Extract	205	$7,675.63	$9.56	$0.00	28.5	62.6	0	8	$297.54	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	QUETIAPINE FUMARATE	5915	NA	HYDROCO/APAP TAB 10-325MG	DIBENZAPINES**	Extract	124	$4,373.23	$12.73	$0.00	33.1	54.1	0	9	$184.52	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	5710	NA	OXYCOD/APAP TAB 10-325MG	BENZODIAZEPINES**	Extract	117	$4,926.73	$10.49	$0.00	29.6	70.8	0	7	$235.46	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	PANTOPRAZOLE SODIUM	4927	NA	CLOPIDOGREL TAB 75MG	PROTON PUMP INHIBITORS**	Extract	113	$1,743.51	$8.51	$0.00	44.1	44.5	0	12	$267.62	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	HYDROCODONE/ACETAMINOPHEN	6599	NA	ALPRAZOLAM TAB 1MG	OPIOID COMBINATIONS**	Extract	109	$6,723.53	$16.38	$0.00	27.8	96.5	0	2	$144.49	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	IBUPROFEN	6610	NA	SERTRALINE TAB 100MG	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Extract	108	$2,610.04	$13.32	$0.00	25.0	69.6	0	9	$197.22	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	ASPIRIN LOW STRENGTH	6410	NA	ENOXAPARIN INJ 40/0.4ML	SALICYLATES**	Message	105	$4.07	$0.02	$0.00	1.0	1.8	0	23	$0.58			
Drug-Drug Interaction (DDI-DTMS)	LISINOPRIL	3610	NA	SPIRONOLACT TAB 25MG	ACE INHIBITORS**	Extract	100	$1,748.58	$9.45	$0.00	67.2	72.6	0	11	$158.26	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	CLOPIDOGREL	8515	NA	PANTOPRAZOLE TAB 40MG	PLATELET AGGREGATION INHIBITORS**	Extract	96	$1,747.48	$9.30	$0.00	43.9	44.5	0	14	$262.90	DD,M0,1G		
Drug-Drug Interaction (DDI-DTMS)	IBUPROFEN	6610	NA	SERTRALINE TAB 50MG	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Extract	95	$2,106.46	$12.06	$0.00	21.8	60.0	0	8	$181.86	DD,M0,1G		
Duplicate Rx (DUPRX)	HYDROCODONE/ACETAMINOPHEN	6599	NA	HYDROCO/APAP TAB 10-325MG	OPIOID COMBINATIONS**	Hard Reject	4	$5,332.65	$22.50	$0.00	30.0	118.8	275	5	$105.91			
Duplicate Rx (DUPRX)	PROVENTIL HFA	4420	NA	PROVENTIL AER HFA	SYMPATHOMIMETICS**	Soft Reject	1	$31,668.24	$86.70	$0.00	25.0	6.7	361	0				
Duplicate Rx (DUPRX)	ATORVASTATIN CALCIUM	3940	NA	ATORVASTATIN TAB 40MG	HMG COA REDUCTASE INHIBITORS**	Soft Reject	1	$3,777.70	$13.06	$0.00	30.0	30.0	296	0				
Duplicate Rx (DUPRX)	AMLODIPINE BESYLATE	3400	NA	AMLODIPINE TAB 10MG	CALCIUM CHANNEL BLOCKERS**	Soft Reject	1	$2,399.87	$10.49	$0.00	15.0	15.0	268	0				
Duplicate Rx (DUPRX)	SODIUM CHLORIDE	7975	NA	SOD CHLORIDE INJ 0.9%	SODIUM**	Soft Reject	0	$2,377.33					1,183	0				
Duplicate Rx (DUPRX)	EPOGEN	8240	NA	EPOGEN INJ 10000/ML	HEMATOPOIETIC GROWTH FACTORS**	Soft Reject	0	$40,499.65					986	0				
Duplicate Rx (DUPRX)	ONDANSETRON HYDROCHLORIDE	5025	NA	ONDANSETRON INJ 4MG/2ML	5-HT3 RECEPTOR ANTAGONISTS**	Soft Reject	0	$318.43					441	0				
Duplicate Rx (DUPRX)	GABAPENTIN	7260	NA	GABAPENTIN CAP 300MG	ANTICONVULSANTS - MISC.**	Soft Reject	0	$5,078.64					368	0				
Duplicate Rx (DUPRX)	HECTOROL	3090	NA	HECTOROL INJ 4MCG/2ML	METABOLIC MODIFIERS**	Soft Reject	0	$1,582.35					314	0				
Duplicate Rx (DUPRX)	PANTOPRAZOLE SODIUM	4927	NA	PANTOPRAZOLE TAB 40MG	PROTON PUMP INHIBITORS**	Soft Reject	0	$2,502.38					267	0				
Duplicate Therapy (DUPTHER)	QUETIAPINE FUMARATE	5915	NA	ORAL ANTIPSYCHOTICS	DIBENZAPINES**	Extract	678	$15,877.93	$12.72	$0.00	31.4	42.9	0	54	$1,701.93	TD,M0,1G		
Duplicate Therapy (DUPTHER)	KETOROLAC TROMETHAMINE	6610	NA	NON-STEROIDAL ANTI-INFLAMMATOR	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Message	676	$4,915.63	$5.79	$0.00	1.0	1.9	0	7	$51.26			
Duplicate Therapy (DUPTHER)	MORPHINE SULFATE	6510	NA	SHORT ACTING NARCOTIC ANALGESI	OPIOID AGONISTS**	Message	573	$2,875.50	$3.15	$0.00	1.0	1.8	0	21	$85.46			
Duplicate Therapy (DUPTHER)	RISPERIDONE	5907	NA	ORAL ANTIPSYCHOTICS	BENZISOXAZOLES**	Extract	468	$9,815.50	$11.74	$0.00	31.9	52.3	0	47	$1,146.41	TD,M0,1G		
Duplicate Therapy (DUPTHER)	DEXAMETHASONE SODIUM PHOSPHATE	2210	NA	GLUCOCORTICOSTEROIDS	GLUCOCORTICOSTEROIDS**	Message	320	$2,778.29	$6.79	$0.00	1.0	4.7	0	8	$26.87			
Duplicate Therapy (DUPTHER)	GABAPENTIN	7260	NA	GABAPENTIN AND RELATED	ANTICONVULSANTS - MISC.**	Extract	301	$10,889.44	$16.14	$0.00	36.6	109.7	0	66	$2,227.70	TD,M0,1G		
Duplicate Therapy (DUPTHER)	ARIPIPRAZOLE	5925	NA	ORAL ANTIPSYCHOTICS	QUINOLINONE DERIVATIVES**	Extract	277	$12,413.57	$21.14	$0.00	30.4	33.7	0	42	$1,968.05	TD,M0,1G		
Duplicate Therapy (DUPTHER)	OLANZAPINE	5915	NA	ORAL ANTIPSYCHOTICS	DIBENZAPINES**	Extract	275	$7,319.60	$13.57	$0.00	29.7	37.2	0	37	$1,044.90	TD,M0,1G		
Duplicate Therapy (DUPTHER)	LEVOTHYROXINE SODIUM	2810	NA	THYROID HORMONES	THYROID HORMONES**	Extract	272	$8,181.59	$16.81	$0.00	58.2	57.7	0	56	$1,820.26	TD,M0,1G		
Duplicate Therapy (DUPTHER)	LISINOPRIL	3610	NA	ANGIOTENSIN BLOCKERS	ACE INHIBITORS**	Extract	240	$4,636.47	$9.17	$0.00	62.3	66.9	0	54	$845.55	TD,M0,1G		

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending, total Reversal Rxs descending and Top Drug/Client Rider ascending.

Total	**12,887**	**$286,229.26**	**$1,384.06**	**$0.00**	**1,172.0**	**2,456.667**	**4,759**	**1,055**	**$26,371.78**			

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending, total Reversal Rxs descending and Top Drug/Client Rider ascending.

RXT6050D - Summarized DUR Activity Report

From 10/1/19 Through 12/31/19

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): NVM-NEVADA MEDICAID

Group(s): ALL

Date Type:	Date Filled
Start Date:	2019-10-01
End Date:	2019-12-31
Relative Description:	Select Date Range
Top Values to Display:	10
cDUR Edit Types:	-, ACTMAINT, ALLERCHK, COMPLIAN, DDI-DTMS, DIAGCAUT, DINFERRD, DOSECHEK, DRUG_AGE, DRUG_SEX, DUPRX, DUPTHER, MEDLIMIT, THERDOSE
Display Report Description:	No

Nevada Medicaid

Retro-DUR Activities
Fee for Service
Quarter 4, 2019

Date	Type	Sent	Responses	Prescribers	Recipients
Nov-19	Triptan wPreventative	31	7	29	31
Dec-19	Hep C Treatement Completed	149	46	53	149