Nevada Medicaid Drug Use Review Board Meeting

October 22, 2020

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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	September 14, 2020
Date of Meeting:	Thursday, October 22, 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).
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=ef129d72361979974b6b8cf7002af797b Out of deference to Declaration of Emergency Directive 006 (https://nvhealthresponse.nv.gov/wpcontent/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 on March 22, 2020 & Emergency Directive 003 (https://nvhealthresponse.nv.gov/wpcontent/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. 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. 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 Tanya Benitez at tbenitez@dhcfp.nv.gov 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.*
Event Number:	171 082 7989 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.

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For Audio Only:

Phone: (763) 957-6300
Event: 171 082 7989

PLEASE DO NOT PUT THIS NUMBER ON HOLD (*hang up and rejoin if you must take another call*)

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

(*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.* **Note: this guidance regarding public comment applies throughout this agenda where public comment is referenced.**

Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).)

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from July 23, 2020.
b. Status Update by DHCFP.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical antipruritics.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. 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 multiple sclerosis (MS) agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.

iv. 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 gonadotropin-releasing hormone (GnRH)/luteinizing hormone-releasing hormone (LHRH) antagonists and combinations.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for bone density regulators.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

5. DUR Board Requested Reports

a. **For Possible Action**: Opioid utilization – top prescribers and members.

i. Discussion by the Board and review of utilization data.
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.

b. **For Possible Action**: Opioid utilization in combination with benzodiazepines.

i. Discussion by the Board and review of utilization data.
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.

c. **For Possible Action**: Gabapentin and pregabalin utilization

i. Discussion by the Board and review of utilization data.
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.

6. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q1 2020 and Q2 2020 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q2 2020.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

i. Status of previous quarter.
ii. Status of current quarter.
iii. Review and discussion of responses.

7. Centers for Medicare and Medicaid Services (CMS) Annual Drug Utilization Review Surveys

a. Fee-for-Service Annual DUR Survey presented by OptumRx.
b. Anthem Blue Cross Blue Shield Healthcare Solutions Annual DUR Survey presentation.
c. Health Plan of Nevada (HPN) Annual DUR Survey presentation.
d. SilverSummit Healthplan Annual DUR Survey presentation.

8. Closing Discussion

a. Public comment.
(No action may be taken upon a matter raised under public comment period unless the matter itself has been specifically included on an agenda as an action item. Comments will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record and to spell their last name and provide the secretary with written comments.)

b. **For Possible Action**: Date and location of the next meeting.

c. Adjournment.

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

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 DHCFP. 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.

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 DHCFP 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	Dave England, Pharm.D.
Netochi Adeolokun, Pharm.D., Vice Chair	Mohammad Khan, MD
Mark Canty, MD	Brian Le, DO
Crystal Castaneda, MD	Michael Owens, MD
Jessica Cate, Pharm.D.	Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2020

Date	Time	Location
October 22, 2020	1:00 PM	On-line

Drug Use Review (DUR) Board Meeting Schedule for 2021

Date	Time	Location
January 28, 2021	1:00 PM	TBD
April 22, 2021	1:00 PM	TBD
July 22, 2021	1:00 PM	TBD
October 14, 2021	1:00 PM	TBD

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

Draft Meeting Minutes

Date of Meeting:	Thursday, July 23, 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/wpcontent/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/wpcontent/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.

ATTENDEES

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

Board Members Absent
Crystal Castaneda, MD
Michael Owens, MD

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
Ellen Flowers, Program Officer

DXC
Jovanna Leid, Pharm.D.

OptumRx
Carl Jeffery, Pharm.D.
Daniel Medina
Sean Hansen

Managed Care Organizations
Thomas Beranek – Silver Summit Health Plan
Ryan Bitton – Health Plan of Nevada
Lisa Todd – Anthem
Luke Lim – Anthem

Public
Kevin Aholt
David Armstrong, Ascendis Pharmaceuticals, Inc.
Jeanette Belz, J. K Belz and Associates
Kenneth Berry, Alkermes
Scott Budsberg, Amgen
Betty Chan, Gilead Sciences
Jeana Colabianchi, Sunovion
Christopher Dobberpuhl, Ascendis Pharma
Leslie Dixon, Nevada Psychiatric Association
Ben Droese, Amgen
Mark Duerre
Michelle Duke, Genentech
Lisa Durette, Nevada Council on Child and Adolescent Psychiatry
Joe Ferroli
Allison Genco
Becky Gonzales
Kathy Howard, Scilex Pharmaceuticals
Steve Isaki, Lundbeck
Camille Kerr
Sapandeep Khurana
Chi Kohlhoff, Viela Bio
Jimmy Lau
Lori McDermott, Supernus
Brian McKenna, Tricida
Margot Miglins, Amgen
Hector Mobine, Amgen
Valerie Ng
Hiten Patadia
Warner Quon Quon, Ascendis
Carol Ricciotti
Lovell Robinson, Abbvie
Nicole Robling
Amy Rodenburg, Abbvie
Deborah Sheppe, Neurelis
Tom Telly, Ascendis Pharma
Samantha Ward
Michael Zarob, Alkermes

AGENDA

1. Call to Order and Roll Call

Jennifer Wheeler, Chair: The time is 1:08 and I will call the meeting to order. This is the Drug Use Review Board and it is July 23rd. I will start with a roll call.

Netochi Adeolokun: Netochi Adeolokun, pharmacist in Reno.

Mark Canty: Mark Canty, family medicine in Reno.

Jessica Cate: Jessica Cate, pharmacist in Reno.

Dave England: Dave England, pharmacist in Las Vegas.

Mohammad Khan: Mohammad Khan, psychiatrist in Las Vegas.

Brian Le: Brian Le, physician in Las Vegas.

Jim Tran: Jim Tran, pharmacist in Las Vegas.

Jennifer Wheeler, Chair: Jennifer Wheeler, pharmacist in Reno.

Holly Long: Can we do roll call for the State too?

Jennifer Wheeler, Chair: Yes, go ahead.

Holly Long: Holly Long with DHCFP.

DuAne Young: DuAne Young, Deputy Administrator, Nevada Medicaid.

Beth Slamowitz: Beth Slamowitz with the Director's office.

Homa Woodrum: Homa Woodrum, Deputy Attorney General for the State of Nevada.

Holly Long: Could the Managed Care Organizations introduce yourselves? Lisa, we can start with you.

Lisa Todd: Lisa Todd with Anthem.

Ryan Bitton: Ryan Bitton with Health Plan of Nevada.

Tom Beranek: Tom Beranek with SilverSummit Health Plan.

2. Public Comment on Any Matter on the Agenda

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from April 30, 2020

Jennifer Wheeler, Chair: Can we get a motion to approve the minutes from the last meeting?

Motion and second to approve the meeting minutes as presented.

Voting: Ayes are unanimous, the motion carries.

b. Status Update by the DHCFP

Holly Long: My name is Holly Long; I am a Social Services Program Specialist for Pharmacy Services at the DHCFP. I have a couple of brief updates and then I will turn it over to our Deputy Administrator Duane Young who will also provide a DHCFP update. First, the DHCFP will be presenting the proposed revisions to MSM Chapter 1200 at the public hearing next week on July 28. The presentation will include the approved changes from the January DUR meeting, updates to Epclusa policy based on FDA revised age indication and revisions to the diabetic supply program policy. The DHCFP has submitted the annual CMS State Survey to CMS and I am waiting for approval or any questions and feedback from CMS. The Fee-for-Service and MCO Surveys will be presented at the next meeting in October. The 2021 meeting schedule for DUR and Silver State Scripts Board has been posted on the DHCFP Pharmacy Services and medicaid.nv.gov sites. We are planning on continuing to have meetings held via WebEx until further notification. I want to welcome a new board member, but she is unable to participate today. Dr. Crystal Casteneda has been appointed to the DUR Board. We will introduce her again when she is able to attend.

I also want to welcome a new Anthem Managed Care Organization representative, Luke Lim. He will be taking over for Lisa Todd. It is sad to say this is Lisa's last meeting with us, but we are looking forward to working with Luke. I am going to turn it over now to DuAne Young.

DuAne Young: This is DuAne Young and I serve as the Deputy Administrator over programs for the Division. I just want to briefly speak to you today. As many of you are aware, we just came out of the special legislative session that was called to resolve the unprecedented budget issues that the state is facing. If any of you had a chance to watch going into the session, we knew that we are facing very significant challenges in terms of funding. Medicaid being one of the largest programs, along with education, were put at the forefront with presentations to both the committees of the whole of the Senate and the Assembly. Each day we answered about two hours' worth of questions, as well as follow up questions all the way through the end of Sunday. As a result of that, what was initially proposed going in, we were allowed to keep all our optional services and services that are considered optional through the Centers for Medicare and Medicaid Services. We were able to keep those services, however, there will be a six percent rate reduction across the board to all providers for Medicaid. The only exemption to this is those providers who are cost-based in their reimbursement. Meaning that their annual rates are based on their yearly cost report. With that, there are also some rate increases that were provided in the 2019 80th session, and those were reduced as well for the neonatal intensive care units as well as the rates that were given to the hospitals as the acute increase. Those were walked back as well. There were also some mitigations that were put in place as cost-saving measures. One of those directly impacting pharmacy is the creation of a specialty pharmacy that the Division is working on now, with the hopes of launching at the beginning of 2021. I think that as you all are aware, we are in a unique and interesting time in Nevada's history. The discussion will lead us into the regular session coming up in February about how to look at more revenue streams for the state as a way to restore some of the cuts that happened in this special session and to continue along the path that we were on before the pandemic, which was to continue to bolster and build Medicaid. I know that was a lot of information. There is an opportunity to submit some questions through the chat box and if we can address them today, we will or feel free to reach out to one of the Medicaid staff. I will pause to take any questions from the board. Thank you.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for psychotropic medications for children and adolescents.

Jennifer Wheeler, Chair: Thank you. I will open it for general public comment. Hearing none, we can move to our clinical presentation. The first on Page 44 of the binder is reviewing the psychotropic medications in children and adolescents.

Carl Jeffery: This class was requested to be reviewed by some of the physicians in the community. We created this policy in September of 2015. We worked closely with several of the psychiatrists in the area and I think it has been successful. I think we do have some of the psychiatrists on the phone, we can open the line for public comment.

Lisa Durette: Hello, this is Dr. Lisa Durette, I am currently the president of the Nevada Council on Child and Adolescent Psychiatry. I am also an assistant professor of psychiatry for the UNLV School of Medicine and serve as the Training Director for Child and Adolescent Psychiatry here in Las Vegas. I am going to read a statement and make a recommendation that pertains to the proposed prior authorization

document that I read through. Child and adolescent psychiatrists strive to provide effective and safe treatment to children incorporating evidence-based practices and patient-centered care while recognizing the need to reduce costs associated with care delivery. Current prior authorization procedures require time and effort by child psychiatrists an undersupplied specialty needed for safe prescribing of psychotropic medications to children with psychiatric disorders. This process often takes significant time, which is unreimbursed, away from direct patient care. The 2017 Medical Association Survey found the average physician spends 14.6 hours a week processing prior authorizations. Administrative burdens associated with prior authorization processes can interfere with the ability of a child and adolescent psychiatrist to treat patients of high complexity. Prior authorization procedures may result in determinations that restrict a child's access to clinically necessary treatment. According to surveys, 78% of physicians reported that patients abandon treatment when waiting for prior authorizations to be completed. These factors degrade the quality and increase the overall cost of care. Undertreated psychiatric disorders and increased medical costs for children and their parents. The American Academy of Child and Adolescent Psychiatry has joined numerous medical organizations and insurers in endorsing prior authorizations and utilization management reform principles, which are publicly available on the American Medical Associations website. In reference to this proposed prior authorization, I strongly recommend that the state of Nevada's Drug Utilization Review Board makes the recommendation that board-certified child and adolescent psychiatrists of which there are currently only 41 in the state of Nevada, which is publicly available on the American Board of Psychiatry and Neurology website, be exempt from prior authorizations for psychiatric medications to allow for access to care for the youth that we treat. That is all I have to say. I'm happy to answer any questions.

Sapandeep Khurana: Thank you, I am a child and adolescent psychiatrist, I work in Las Vegas and for rural Nevada and I am actively involved in the training of child and adolescent psychiatrists. I see a lot of Nevada Medicaid recipients and most of these people by the time they come to us, they have not been adequately managed. I will echo what Dr. Durrett said in that these patients are vastly underserved. I would request the board consider exempting board-certified child psychiatrists from these criteria just like Neurology is exempt from epilepsy treatments.

Carl Jeffery: I don’t hear any other public comment, so I will go ahead with the overview. The psychotropics in children policy really boils down to polypharmacy. The classes include antipsychotics, antidepressants, mood stabilizers, including anticonvulsants, sedative-hypnotics and antianxiety agents. The PA really only applies if the child is under six years of age or for polypharmacy. This is defined as intra-class where more than one drug within the same therapeutic class within 60 days is prescribed. Or inter-class is more than one drug across the different therapeutic classes within a 60-day time period. A PA is required for four or more drugs across all listed therapeutic classes. There is an exception for anticonvulsants if the prescriber is listed as a neurologist and there is a diagnosis of seizure disorder on the prescription. Looking at utilization for all children under 18 years of age. We do not have that many on a lot of agents. In 2015, there were quite a few children on all five classes, now there are only five children on all five classes. The classes are broken down further to show what the most commonly prescribed agents are within each class. I will turn it over to Anthem and Lisa to speak to their data.

Lisa Todd: We do not oppose the criteria Optum is proposing. The utilization breakdown is similar. For antidepressants, there are no children five and under. On antipsychotics, there was a small amount under the age of six. Sedative hypnotics and anticonvulsants are shown there.

Ryan Bitton: We are also in approval of what was proposed by Optum. We have a similar set up with age limits. The utilization is similar, it is broken down by age bracket and by month and drug.

Tom Beranek: The data is pretty much the same for us. We agree with the recommendations for the policy. Our data looks a little different, it is in alphabetical order. Nothing really to call out.

Jennifer Wheeler, Chair: Any discussion from the board?

Mohammad Khan: Being a Board-Certified Psychiatrist, recognizing the deficiency in the number of providers in the State, I think in the spirit of parity, it makes sense to allow a similar exemption for board-certified child psychiatrists.

Carl Jeffery: Currently there is coding set to exempt neurologists when prescribing anticonvulsants when there is a diagnosis of a seizure disorder on the claim and ADD and ADHD medication PAs are bypassed for psychiatrists with a diagnosis of ADD or ADHD submitted on the claim for members under age 18.

Jennifer Wheeler, Chair: There would be a special code for board-certified child psychiatrists?

Carl Jeffery: In the system, we have them set up for ADD and ADHD, we have a list of physicians that are identified as psychiatrists.

Holly Long: I like to look at what other states are doing. When I reached out to the other states, they commented that they have copied this policy for their own. So I did not receive any other feedback from other states.

Brian Le: I agree with Dr. Khan. As a practicing physician, I think the prior authorizations can take a lot of time from the office. I think if it is possible, we should make it easier for psychiatrists to prescribe. My concern is benzodiazepines.

Carl Jeffery: I will try to summarize this in a comment on the policy. The board wished to add an exception for all five classes of psychotropics? No polypharmacy rules would apply for the psychiatrists we have listed in our system.

Mohammad Khan: Yes, that is what I would support.

Holly Long: I want to emphasize to the board and everyone listening, currently no PA is needed unless it is polypharmacy or unless the child is under six years of age.

Carl Jeffery: You are right, there is no PA needed for the first agent within a class for up to three different classes. The fourth agent requires PA. I'm displaying on the screen the existing policy. What I hear is a wish to add an exception to the criteria for all classes for psychiatrists. Are we just adding child psychiatry or just psychiatry?

Mohammad Khan: I would limit it to child psychiatrists.

Jennifer Wheeler, Chair: Does anyone have feedback on the multiple benzodiazepines? Looking at the utilization, it looks like patients that fall in that category are on multiple agents.

Holly Long: What happens if a child comes out of a facility seeing a different psychiatrist, are we going to be stuck with polypharmacy occurring and not be able to catch it?

Carl Jeffery: If the member is transitioning care and coming from the care of a regular psychiatrist, it would not be a child psychiatrist, I think a PA would be applied.

Beth Slamowitz: When we went through all the conversations to put the polypharmacy and PA requirements in place, there was no concern about a child under the care of a psychiatrist or child psychiatrist. The concern was multiple prescribers like children in foster care. There were instances of multiple prescribers maybe not knowing what the others are doing resulting in polypharmacy. My concern is if we exempt child psychiatrists, we may not catch the kids that are seeing more than one physician.

Carl Jeffery: I think that is a valid point. Does the board have any comments?

Jennifer Wheeler, Chair: I agree, it concerns me. Some of these kids do not always go to the same pharmacy. When you get multiple providers and multiple pharmacies, you are not catching these interactions.

Dave England: I also agree. I think having an exception for some specialists is ok, but once we have a couple of specialists involved, then the PA should be reimplemented.

Jennifer Wheeler, Chair: What about a limit on polypharmacy? Like no more than three without a PA? Any other ideas or feedback?

Beth Slamowitz: I think that is how the policy currently stands. Our intent when this was put in place was not to burden providers with PAs. The policy was focused on polypharmacy. To Dave's point, from a system standpoint it would be difficult and cumbersome to apply prior authorization criteria when there are multiple prescribers.

Mohammad Khan: To me, that sounds like more of a pharmacy issue than a prescriber issue. If somebody is going to a pharmacy with multiple prescriptions from different prescribers, it is part of the clinical care to find out what medications someone is on and what should be continued or discontinued. I would think the pharmacy would only be filling prescriptions ordered by a child psychiatrist.

Jennifer Wheeler, Chair: That is assuming the patient uses the same pharmacy, that is not always the case. And the pharmacists do not always know the specific specialties of the prescribers.

Beth Slamowitz: Jen, to your point, often the retail chains have connected systems and a pharmacist is able to catch some duplication. And the insurance may notify the pharmacy of a duplication, but that is dependent on their system. I agree a prescribing physician should have complete authority and control. But there is always one bad apple that is not checking or does not have the appropriate EMR to do so. We have the current rules in place to help with this. We did see a large spike in medication being used in this population. I have a huge concern opening it wide open like that.

Netochi Adeolokun: I would like to recap my understanding. We are trying to apply the same exception for board-certified child psychiatrists as the same exemption as the neurologists. Do the neurologists have a limit on how much they could prescribe in regards to drugs in the same class without polypharmacy PA?

Carl Jeffery: Their policy is only for the anticonvulsants and there is no limit on the number they can prescribe.

Netochi Adeolokun: Can we keep the same exception for the child psychiatrists just for anticonvulsants?

Carl Jeffery: We can narrow it down to certain classes. Maybe as a compromise we add the exception to antipsychotics, anticonvulsants and antidepressants. That would leave anxiolytics and sedative-hypnotics would still be limited.

Mohammad Khan: That would exclude benzos? Any other classes?

Carl Jeffery: That would include benzos and sedative-hypnotics like Ambien and hydroxyzine would have the polypharmacy restriction applied even for child psychiatrists.

Mohammad Khan: That sounds reasonable to me.

Jennifer Wheeler, Chair: I like that a lot better. Any other feedback from the Board?

Carl Jeffery: I updated the information here to say the polypharmacy rules could be bypassed for antidepressants, anticonvulsants only if the prescriber is a board-certified child psychiatrist.

Jessica Cate: I think mood stabilizers should also be bypassed.

Carl Jeffery: Yes, those fall into the anticonvulsants, but we can clarify that.

Jennifer Wheeler, Chair: We are asking for a motion to approve how it is presented on the screen with a change of, "polypharmacy rules would be bypassed for antidepressants, antipsychotics, anticonvulsants and mood stabilizers if the prescriber is a board-certified child psychiatrist."

Motion and second to approve as presented.

Mohammad Khan: Can we add ADHD drugs to this category?

Carl Jeffery: ADHD is already excluded if the diagnosis of ADHD is on the claim and the prescriber is a psychiatrist.

Voting: Ayes are unanimous, the motion carries.

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

Jennifer Wheeler, Chair: The next item is Fibromyalgia agents. I will open it for public comment.

Carl Jeffery: The medication is Savella we are discussing today. In our continued efforts to review old guidelines, we next have Savella criteria. This was last reviewed by the board on June 3, 2010. The criteria are straightforward with just the diagnosis of fibromyalgia or myalgia and myositis. If this is on the claim from the pharmacy, the PA requirement will be bypassed. We really do not see very much utilization on this medication, maybe 15 claims per month. Savella still only has the indication for management of fibromyalgia. I do not think we need to make any changes to this at this time.

Lisa Todd: We agree with Optum's proposal. We have a low volume too, only nine members on a regular basis.

Ryan Bitton: We also approve the criteria as submitted. We have less than 10 and it has dropped off in the past six months.

Tom Beranek: I did make a couple of recommendations. We added a failure of duloxetine for at least 180 days before approving. And failure or intolerance to a 30-day trial of a tricyclic antidepressant or cyclobenzaprine. I like to have dose limits as well. We did not have much utilization either, maybe 16 total members in the past year.

Jennifer Wheeler, Chair: Any comments from the Board? Can I get a motion to approve the prior authorization criteria?

Motion and second to accept the criteria as presented.

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 osteoporosis agents.

Jennifer Wheeler, Chair: Next we have osteoporosis agents, Forteo and Prolia. Do we have any public comment?

Ben Droese: This is Ben Droese, I am a Health Outcomes and Pharmacoeconomics Specialist with Amgen Medical Affairs. Thank you for the opportunity to provide clinical updates on Prolia and Evenity. As shown in the meeting binder, Prolia is indicated for several populations including postmenopausal osteoporosis, male osteoporosis, patients with breast or prostate cancer receiving hormone therapy, and most recently, approved for the treatment of glucocorticoid-induced osteoporosis in patients at high risk of fracture. I respectfully request the glucocorticoid-induced osteoporosis indication be added to the Prolia coverage policy. In addition, I would like to note a label update regarding the risk of multiple vertebral fractures following Prolia discontinuations. Language has been updated to clearly indicate that if Prolia is discontinued, patients should be transitioned to an alternative antiresorptive therapy. Another important update is the recently published guidelines on the treatment of postmenopausal osteoporosis from the American Association of Clinical Endocrinology, which includes recommendations for Prolia as an initial treatment option for patients at high risk of fracture. Evenity is also included in the recent guidelines as an initial treatment option for patients with a very high risk of fracture. Please note Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture.

Jennifer Wheeler, Chair: Any other public comment?

Carl Jeffery: For the Osteoporosis agents, there are two agents in this class included for discussion today, Forteo and Prolia. Both these criteria were last reviewed in October 2012. We have a slight update to the Forteo criteria, to add on number four, “or the recipient has had esophagitis, or the recipient is unable to remain upright.” We do not have proposed changes to the Prolia criteria. I will provide just a quick overview of osteoporosis and the treatment with these medications. Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture. In 2010, more than two million osteoporosis-related fractures occur annually with more than 70% occurring in women. By age 60, half of white women have osteopenia or osteoporosis. The general recommendation is still calcium supplements and vitamin D and regular weight-bearing exercise. Bisphosphonates are the mainstay in therapy, but parathyroid hormone analogs such as Forteo and receptor activator of nuclear factor K-B ligand inhibitors such as Prolia are used in high-risk patients. Utilization has not been high for Forteo, six members and 16 total claims in the past year. Prolia sees a few more, 158 members and 225 claims over the past year. Forteo is a once-daily subcutaneous shot and Prolia is an every six-month subcutaneous shot, so a little more convenient. I know Ben mentioned some updates to the indications for Prolia. The criteria we currently have are for postmenopausal osteoporosis, male osteoporosis, and non-metastatic prostate and breast cancer. We will have to take it back to get some criteria specific to the new indications.

Jennifer Wheeler, Chair: Do you want to do that for the next meeting and hold off for now?

Carl Jeffery: We can certainly do that if that is what the board wants. We can include some of the other newer agents then, as well.

Jennifer Wheeler, Chair: Does anyone on the Board have any comment on this? Can we get a motion to approve additional criteria at the next meeting?

Motion and second to bring the topic back to the next meeting.

Voting: Ayes are unanimous, the motion carries.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for anti-lipidemic agents – PCSK9 inhibitors.

Jennifer Wheeler, Chair: The next class is the PCSK9 inhibitors. Is there any public comment?

Ben Droese: Thanks again, I'm Ben Droese, the Health Outcomes Pharmacoeconomics Specialist with Amgen. As a reminder, Repatha is indicated to reduce MI and stroke and coronary revascularization in patients with established cardiovascular disease, as well as indicated for LDL reduction in patients with primary hyperlipidemia and homozygous FH. Please consider allowing non-specialists such as primary care and advanced practice providers to provide care by removing the specialist requirement.

Jennifer Wheeler, Chair: Thank you, any other public comment?

Carl Jeffery: The PCSK9 inhibitors were last reviewed in January 2016. I think when these first hit the market, they were supposed to be the magic bullet for cardiovascular disease. But the utilization does not reflect this. I think we all know the consequences and the toll cardiovascular disease is taking in the US. Praluent and Repatha are fully human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 or PCSK9. PCSK9 is an enzyme that leads to the degradation of hepatocyte LDL-C receptor, which results in increased LDL-C levels. By inhibiting PCSK9, LDL receptor recycling is preserved, and LDL-C levels are subsequently reduced. These products are administered SQ every two weeks or once monthly. Guidelines suggest a PCSK9 after maximally tolerated statin doses with ezetimibe. Outcomes studies have demonstrated a slight reduction in CV events, but the benefit on mortality is unclear. Optum does not have any proposed changes to the current criteria. The utilization is pretty low with this class and we have not heard any complaints about the current criteria. Ben was asking us to remove the specialist requirement and add a Zetia requirement.

Lisa Todd: We are not opposed to the criteria presented. Our utilization is low, 15 members on Repatha and two on Praluent.

Ryan Bitton: We approve the presented criteria. We just added a validation of the diagnosis and pretreatment of LDL levels. We have more on PCSK9s, mostly Repatha.

Tom Beranek: We approve the criteria as presented. We had 29 claims over the one-year period.

Jennifer Wheeler, Chair: Thank you, any comment from the Board?

Netochi Adeolokun: Are we proposing to remove the "in consultation with a cardiologist?" I do like the idea of removing the specialist requirement. If a patient has CVD or an MI, their risk of having another is really high. There is a wait time to see a cardiologist, so allowing primary care to start a PCSK9 would be very helpful.

Carl Jeffery: We did not recommend any changes for that. I'm showing the Chapter 1200 with that requirement. It is up to the Board. I think by the time they are at the point of needing an agent like this, they are pretty far along with different therapies and I think it is appropriate to see a lipid specialist or cardiologist.

Jennifer Wheeler, Chair: Does anyone have any comments for removing that or changing the wording?

Dave England: I am fine with the way it is already.

Jessica Cate: I see both sides, but I am inclined to agree with Carl. These patients would likely have been seen by a cardiologist even if they were hospitalized for an MI, they would have seen a cardiologist there. That can be considered a consultation, so we are not delaying care.

Motion and second to accept the criteria as presented.

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 diazepam (Valtoco®) nasal spray.

Jennifer Wheeler, Chair: The next topic is Valtoco Nasal Spray. Do we have any public comment?

Carl Jeffery: We do have some written comments. These were sent to the board prior to the meeting.

Debbie Sheppe: This is Debbie Sheppe from Neurelis. We request to place Valtoco in a preferred position without restrictions. Valtoco is an intranasal formulation of diazepam for emergency rescue treatment of seizure clusters or acute repetitive seizures. It is the first and only nasal rescue treatment for patients with epilepsy down to the age of six. Valtoco was granted orphan drug exclusivity by the FDA on the basis that it demonstrates clinical superiority to diazepam rectal gel. Valtoco provides a non-invasive rescue treatment for seizure emergencies and is the only nasal spray indicated in patients down to the age of six.

Jennifer Wheeler, Chair: Any other public comment?

Carl Jeffery: Valtoco is a new medication with a similar indication to Nayzilam that we recently reviewed. The indication is for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from the patient's usual seizure pattern in patients with epilepsy in patients six years of age and older. Valtoco is a diazepam nasal spray in 5 and 10 mg per device and a max of up to 20mg between the two devices. A second dose may be administered at least four hours after the initial dose. The max dose and treatment frequency is no more than two doses to treat a single episode and no more than one episode every five days and no more than five episodes per month. The efficacy of Valtoco is based on the relative bioavailability of diazepam rectal gel in healthy adults. Our proposed criteria are pretty straight forward. We ask for the diagnosis and then for the provider to at least consider the diazepam rectal gel and then a max quantity of five episodes per month or 10 doses per month. We do not have any utilization.

Lisa Todd: We agree with Optum's proposed criteria and we do not have any utilization either.

Ryan Bitton: HPN agrees with the recommendation and we do not have utilization.

Tom Beranek: We added an age limit of six years or greater, otherwise we are in alignment with Optum's proposed criteria. We also have no utilization.

Jennifer Wheeler, Chair: Any comment from the board?

Carl Jeffery: I have the criteria pulled up with the Nayzilam that is scheduled to be effective soon. We did add an age limit of at least 12 and then a consultation with a neurologist. I think with this diagnosis, they have likely seen a neurologist, but it would not hurt to add that requirement. Adding the age would be a good idea too.

Dave England: I agree, it would be more consistent with what we did before.

Jennifer Wheeler, Chair: Can I get a motion to approve as presented with adding the age being six years and older and prescribed by or in consultation a neurologist.

Motion and second to accept the criteria as amended.

Voting: Ayes are unanimous, the motion carries.

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

Jennifer Wheeler, Chair: The next item on the agenda is looking at removing criteria from prior authorization on Vivitrol. I will open it for public comment.

Carl Jeffery: We do have one letter from Dr. Dixon advocating for Vivitrol.

Leslie Dixon: This is Leslie Dixon, I am board-certified in Addiction Psychiatry. I wrote the letter from the Nevada Psychiatric Association. I am also representing the addiction community and particularly the company for which I am one of the medical directors, Center for Behavioral Health. Vivitrol is the brand name of the long-acting preparation of naltrexone, which is a pure opioid antagonist. It is not a scheduled drug. It is very effective when used appropriately for keeping patients who have opioid use disorder and alcohol use disorder from using. The problem we have with this proposal is that prior authorization basically gets in the way of treatment for these patients because it is very hard to get them into treatment. If they have to wait for prior authorization to go through, which sometimes can take five to six days, we will lose them. They slip back out into the community and back into their drug use. The drug is in the pharmacy and we do the injections ourselves, so we have to send the prescription over to the pharmacy and they have to send it back to us after the insurance has approved it. We are opposed to the prior authorization because it slows treatment and contributes to relapse.

Jennifer Wheeler, Chair: Thank you. Any other public comment?

Ken Berry: This is Ken Berry with Alkermes. I am a pharmacist and a Medical Science Director with Alkermes. Vivitrol is a once-monthly extended-release formulation of naltrexone and is indicated for the treatment of OUD and AUD. Thank you for your consideration in opening access for Vivitrol for addiction treatment.

Jennifer Wheeler, Chair: Anyone else?

Carl Jeffery: I think Dr. Dixon stole my notes, I was going to say nearly the same thing. Our proposal is to remove all these criteria because it limits the provider's ability to start therapy at the appropriate time. This is not a medication that is abused. Vivitrol does have indications for both the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. Extended-release IM naltrexone was compared to buprenorphine/naloxone sublingual film. More

induction failures were seen with ER IM naltrexone, however, among patients who were able to successfully initiate treatment, ER IM naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention. Our recommendation is to remove these criteria, so it would be open access.

Lisa Todd: We agree with the idea of removing the criteria, we currently do not have criteria. We have 88 members on this medication currently.

Ryan Bitton: HPN is also supportive of this, we do not have criteria either. We have about 10 claims per month. It does sit on the PDL, but we support not having to jump through the hoop of the PA.

Tom Beranek: We are also in agreement with the proposed criteria. We had 54 claims over the course of the year.

Jennifer Wheeler, Chair: Any comment from the board? Can I get a motion to remove the criteria for the Vivitrol?

Motion and second to remove the criteria for Vivitrol.

Voting: Ayes are unanimous, the motion carries.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for growth hormones.

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

Carl Jeffery: Somavert is the next drug to discuss. We are bringing this because we have received requests for Somavert, but do not have any clinical criteria for approval. Somavert is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum insulin-like growth factor levels. Acromegaly is caused by the pituitary gland producing too much growth hormone, typically leading to enlarged hands and feet as one of the first, most obvious symptoms. Somavert is a growth hormone receptor antagonist dosed between 10 and 30mg once daily SQ after a loading dose given by a healthcare provider. The proposed criteria are pretty straight forward, just following the label except with the addition of a trial of octreotide and prescribed by or in consultation with an endocrinologist.

Lisa Todd: We have low utilization, only have two members on this. We agree with the proposed criteria.

Ryan Bitton: We approve the criteria with just a slight modification. We ask for validation of the diagnosis by showing growth hormone levels or serum IGF levels. For our utilization, we have one patient with two claims.

Tom Beranek: We mostly agree with the proposed criteria. We have an age limit of 18 years or greater, and a loading dose of 40mg and a maintenance dose of 30mg. We do not have any utilization.

Jennifer Wheeler, Chair: I think the age limit might be a good addition. Could I get a motion to approve the criteria as presented with the addition of an age limit that the patient must be 18 years of age or older?

Motion and second to approve the criteria as amended.

Voting: Ayes are unanimous, the motion carries.

5. Public Comment on any DUR Board Requested Report

Jennifer Wheeler, Chair: We can move into the board reports. Is there any public comment on any of the Board requested reports? We can start with the opioid utilization.

6. DUR Board Requested Reports

a. Opioid utilization – top prescribers and members

Carl Jeffery: The opioid utilization continues the same trend downward. It is interesting the total MED continues to decrease, but the total MED per day supply is flat. This indicates to me what is likely happening is fewer recipients are getting started on opioids, which I think is a good thing. But the recipients already on opioids are maintaining the same MED. Some other states are starting to ratchet down the high utilizers that may have been on opioids for a long period of time. They are mostly using edits at the point of sale, but we could also use the retro-DUR letters to the providers. I do not think letters are going to help decrease the utilization; however, I think the providers know they are prescribing a high dose.

Dave England: I think looking at the MED, we are seeing a flatter line and that is what we want to see. I am happy with this data.

Carl Jeffery: You are referring to the MED per day supply, it does fluctuate a little, but it is zoomed in, but we are seeing a slight decrease in the trend. The next report is broken down by member with the breakdown showing the products the members are on. That is all we have for requested reports, but if there is anything else you see in the community that would be useful, we are always looking for ideas.

Brian Le: I would like to see a report of members on both an opiate and a benzo. How many are still on both medications together?

Carl Jeffery: Ok, we have looked at that before and I think it is worth revisiting.

Lisa Todd: Anthem data is pretty flat as well. The MME did go down just a little bit. I compared two quarters of the top opioid providers by claim volume. I highlighted in yellow the repeat providers, they are in the top 10 in both quarters. The next report is the top 10 utilizers, the member is on the top, then the drug, then the provider. There is only one provider in the top 10 providers that is prescribing for a top 10 member.

Ryan Bitton: HPN has similar reports and trends over time. The MME total is very similar to Fee-for-Service. We do not have MME per day, but we will add that next time. The top 10 providers show three additional providers in quarter four. The next pages are the top 25 members. We highlighted the members seen by the top 10 providers.

Tom Beranek: SilverSummit is similar to the other plans. The member count has not changed much over the year. The claim counts are roughly the same through the year. MME is slightly up, a few months with some upticks, but overall, pretty steady. The top opioid prescribers, there are some new providers in the report now. We are sending benchmark letters to these providers and we sent trifecta letters to eight of these providers. The top 10 members, there really is not much out of the ordinary. One member has a diagnosis of malignant neoplasm and another with lower back pain. Of the 10 members, four of them are prescribed by one of the top 10 prescribers.

7. Public Comment on any Standard DUR Report

Jennifer Wheeler, Chair: Thank you, we will move to standard DUR reports now. Do we have any public comment?

8. Standard DUR Reports

Carl Jeffery: These are the standard reports we see at every meeting. The top medications show anticonvulsants at the top and this has taken over since we ratcheted down on the opioids. I suspect a good portion is Neurontin. Albuterol and SSRI's and then opioids down here on number four. Looking at the paid amount, hemophilia products are always on the top, then antiretrovirals, nothing unusual in the utilization. The concurrent DUR report shows how many claims and interventions occurred for the past quarter. The next page shows the different interactions within the system if they are paid, reversed or rejected. RetroDUR activities include zolpidem for females in March.

Lisa Todd: Our top 10 by paid amount, our drug classes are different than Fee-for-Service, but these are typical and consistent for us. The antiretrovirals include the new HIV meds that are driving up the cost. Of the top 10 drugs by spend, five are the new HIV drugs. Humira is also on the list with a new indication and formulation. On the next report, the top 10 by claim count, the non-steroidal anti-inflammatory agents moved up since we started limiting opioids. This has been consistent over the past few years. The next slide is the prospective DUR. Looking at the top 10 early refills, I was encouraged to see they were not all opioids. They are also consistent. The last piece is retro-DUR. I put one program about education of clinical gaps which includes adherence of cardiovascular drugs.

Ryan Bitton: Our report is in the standard template. The top classes are very similar to Lisa's, with antiretrovirals being up there following by anti-TNF's and insulin. Looking at claim count, this is very similar to what Anthem had shared. The next report shows the retrospective-DUR programs and the outreach efforts. I do not see anything that needs to be called out. On the third page, we have the details of the cardiovascular gaps in care. We had 732 contacts and about 100 responses from providers. The next is another gap in care. The last page is the prospective DUR. Nothing to comment on here.

Tom Beranek: The top 10 drugs classes by paid amount, similar story with antiretrovirals at the top and then insulins and sympathomimetics. The only two differences were the direct factor and the quinolone derivatives from the two quarters. On the top 10 by claim count, nine of the 10 are the same. The non-steroidal and anticonvulsants at the top. The prospective DUR, this is similar to the others. In the retrospective DUR in quarter one, we were working on hypertension non-adherence. We sent 306 letters and received 162 responses.

Jennifer Wheeler, Chair: Thank you, does anyone else have a comment.

Jim Tran: I noticed the gabapentin products. Earlier this year, the FDA put out a warning for abuse potential because it is being used as a booster with opioids. We are seeing a decreasing trend for opioids, but it looks like the gabapentin class is always in the top three. Can we look at the past few months and trend the class to see how it is being prescribed or used?

Carl Jeffery: I think that is something worth looking at. We can add that to the next round of reports.

Holly Long: Do you have any specific parameters or timeframes? I think you said you wanted the past few months, sometimes people like to see several years.

Jim Tran: I don't have any specific parameters, I will welcome any thoughts, but maybe looking back three to six months and trend it to see where it is going.

Lisa Todd: Can we look at the first and second quarters?

Ryan Bitton: I would recommend looking at a longer timeframe. Considering trends with opioids.

Holly Long: I would recommend at least a year. I like looking at three years for trends. Keep in mind when the opioid policy was implemented.

Lisa Todd: I assume we would include pregabalin.

Jim Tran: Yes, gabapentin, and pregabalin. A year is reasonable to review.

Lisa Todd: Do you want the broken down by month so you can see the fluctuation?

Jim Tran: Yes.

9. Closing Discussion

Jennifer Wheeler, Chair: Any other comments? The next meeting is October 22, 2020, virtually at 1:00 PM. The meeting is adjourned.

Clinical Presentations

Prior Authorization Guideline

Guideline Name Topical Antipruritic

1 . Indications

Drug Name: Doxepin Topical
Pruritus: Short-term (≤8 days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus.

2 . Criteria

Product Name: Doxepin Topical	
Approval Length	8 days
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of pruritus with atopic dermatitis or lichen simplex chronicus.

AND

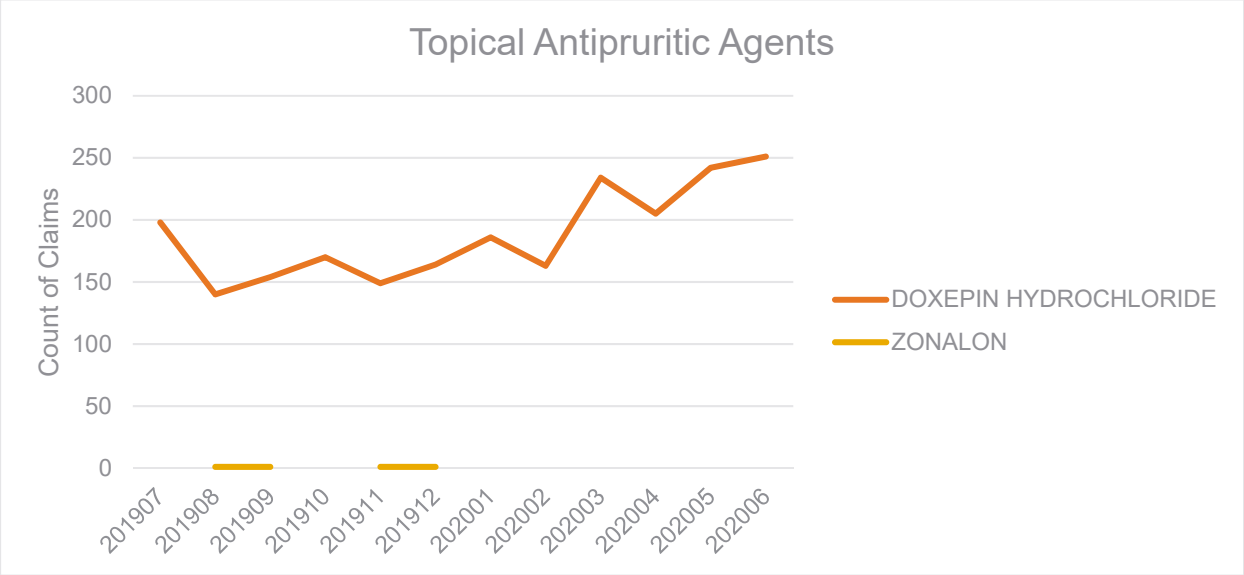
2 - Patient is 18 years of age or older.

AND

3 – Treatment will not exceed 8 days.

Nevada Medicaid
Topical Antipruritic Agents
Fee for Service
July 1, 2019 – June 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
DOXEPIN HYDROCHLORIDE	554	2,256	63,368	286,265
ZONALON	3	7	195	750



INTRODUCTION

- Topical lidocaine is available as single entity and combination products (ie, lidocaine/prilocaine, lidocaine/hydrocortisone, lidocaine/tetracaine). These products are indicated for a number of conditions and are available in multiple dosage forms for topical use (ie, ointment, lotion, gel, cream, jelly, patch, solution) and as an oral solution.
- Lidocaine, prilocaine (amide-type local anesthetics) and tetracaine (ester local anesthetic) produce their analgesic effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium. This action decreases the rate of membrane depolarization and increases the threshold for electrical excitability. The blockage affects all nerve fibers in the following sequence: autonomic, sensory and motor, with effects diminishing in reverse order. Loss of nerve function clinically is as follows: pain, temperature, touch, proprioception, skeletal muscle tone. Direct nerve membrane penetration is necessary for effective anesthesia (*Clinical Pharmacology 2020*).
- Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems; however, the rate and extent of absorption after topical administration is dependent on concentration, total dose, the site of application, and length of exposure. Following topical administration of ointment or jelly, peak effects typically occur within 3 to 5 minutes (*Clinical Pharmacology 2020)*.
- This review focuses on select topical lidocaine products that are available by prescription. Lidocaine products that are used parenterally are not included. Additionally, there are many topical lidocaine products that are available over the counter (OTC); however, the specific brands and availability of OTC products will not be included in this review. To note, many agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Local Anesthetics – Topical and Topical Anesthetic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Doxepin (topical) 5% Cream	✔
lidocaine topical jelly 2%	✔
lidocaine topical gel 2%, 3%, 4%	✔
lidocaine lotion 3%**, 3.5%**	✔
lidocaine topical ointment 5%	✔
lidocaine oral viscous solution 2%	✔
lidocaine HCl topical solution 4%	✔
lidocaine HCl sterile solution 4%	✔
lidocaine topical cream 3%**, 3.25%**, 3.88%**, 4%**, 4.12%**	✔
lidocaine rectal cream 5%**	✔
lidocaine patch 5%	✔
lidocaine topical system 1.8%*	-
Combination Products	
lidocaine-prilocaine cream 2.5-2.5%**	✔
lidocaine-prilocaine cream 2.5-2.5% kits**	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit†	-
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit ‡	-

Drug	Generic Availability
lidocaine-hydrocortisone cream kit 2-2%**,3-0.5%**, 3-1%**, 3-2.5%**	✔
lidocaine-hydrocortisone 2.8-0.55% with aloe gel kit**	✔
lidocaine-tetracaine cream 7-7%	✔

*only available as brand ZTlido
†only available as brand Prizotral
‡only available as brand Prilo Patch Kit
** Disclaimer: This drug has not been found by FDA to be safe and effective, and its labeling has not been approved by the FDA.

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

Table 2. Indications for Single-Entity Products**

Single-Entity Products	Indication
Doxepin cream 5%	Short-term (≤ 8 days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus.
lidocaine jelly	For prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)
lidocaine gel 2%	For the local management of skin wounds, including pressure ulcers, venous stasis ulcers, first and second degree burns, and superficial wounds and scrapes.
lidocaine gel 3%	For the relief of pain, soreness, abrasions, minor burns, insect bites and discomfort due to pruritus, pruritic eczemas, pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine gel 4%	For associated pain, painful wounds and wound healing in either open and closed injuries or conditions. Conditions of pain include topical pain, postsurgical pain and pain associated with various types of closed or open wounds. Conditions of closed wounds include soft tissue and bony injuries caused by contusions, hematomas, crush injuries and sprains/strains due to torsion, traction, compression and/or blunt trauma.
lidocaine lotion 3%	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine lotion 3.5%	For use on normal intact skin for temporary relief of pain and itching due to minor cuts, minor scrapes, minor skin irritations, minor burns and insect bites
lidocaine ointment 5%	• For production of anesthesia of accessible mucous membranes of the oropharynx, • Anesthetic lubricant for intubation • For the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.
lidocaine topical cream 3%, 3.88%, 4%, 4.12%	For the temporary relief of pain and itching associated with minor burns, sunburn, minor cuts, scrapes, insect bites, and minor skin irritation.
lidocaine topical cream 3.25%	For the relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness, and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine rectal cream 5%	Temporary relief of pain and itching due to anorectal disorders
lidocaine patch 5% lidocaine topical system 1.8%	For relief of pain associated with post-herpetic neuralgia (PHN).
lidocaine oral topical solution 2% viscous	For the production of topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx; for reducing gagging during the taking of x-ray pictures and dental impressions

lidocaine HCl sterile solution 4%	For the production of topical anesthesia of the mucous membranes of the respiratory tract or the genito-urinary tract
lidocaine HCl topical solution 4%	For the production of topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(*Prescribing Information: 2% Xylocaine viscous 2014, 4% Xylocaine-MPF 2010, 7T Lido gel 2018, Astero 2016, DermacinRx 2019, Gen7T 2019, Lido-K 2018, lidocaine ointment 5%, lidocaine HCl topical solution 2019, Lidoderm 2018, Lidodose 2018, Lidopin 2014, Lido Rx 2019, LMX4 2019, LMX 5 2018, PharmaPureRx lidocaine HCl 4.12% Cream 2019, Recticare 2019, ZTlido 2018)*

Table 3. Indications for Combination Products**

Combination Products	Indication
lidocaine-prilocaine cream 2.5-2.5%	Used as a topical anesthetic for use on: • Normal intact skin for local analgesia. • Genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.
lidocaine-prilocaine cream 2.5-2.5% kits	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit	
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	
lidocaine-hydrocortisone cream kit	For the anti-inflammatory and anesthetic relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area.
lidocaine-tetracaine cream 7-7%	For use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(*Prescribing Information: Agoneaze 2018, Lido-BDK 2018, lidocaine HCl-hydrocortisone acetate cream 2018, lidocaine HCl-hydrocortisone acetate with aloe gel 2018, Nuvakaan 2019, Pliaglis 2019, Prilo Patch 2019, Prizotral 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

- Topical doxepin has been shown to reduce pruritus in patients with atopic dermatitis.
  - Compared to vehicle alone, relief of pruritus was achieved in 85% of doxepin-treated patients compared to 57% of vehicle-treated patient by day 7. (*Drake et al 1994*)
  - Doxepin has also been shown as an effective treatment for neuropathic pain.
    - A placebo-controlled trial with 151 patients (41 placebo, 41 doxepin, 33 capsaicin, 36 doxepin/capsaicin) demonstrated effective analgesia with all active treatment groups with more rapid effect achieved with the combination of doxepin and capsaicin. (*McCleane et al 2000*)
- Lidocaine/prilocaine has been studied as an anesthetic agent in several settings. Lidocaine products have not consistently shown improvements in pain scores compared to treatment with placebo (*Hopper et al 2014, Minassian et al 2002, Moppett et al 2004*).

- Comparison of various lidocaine formulations to lidocaine/prilocaine creams has demonstrated that they have a similar anesthetic effect (*Herberger et al 2003*, *Koh et al 2004*).
- In an open-label trial of 41 patients, lidocaine-prilocaine 2.5-2.5% cream was found to be significantly more effective than inhalation of a nitrous oxide-oxygen mixture in relieving pain associated with debridement of leg ulcers ($p < 0.001$) (*Claeys et al 2011*).

- Several clinical studies have evaluated the effectiveness of lidocaine-tetracaine cream as a topical anesthetic for many types of laser procedures including pulsed dye, leg vein, non-ablative, facial resurfacing, tattoo removal, and hair removal. Overall, similar results have been found, showing statistically better visual analog score (VAS) pain scores compared to placebo or head-to-head with other topical anesthetics (ie, lidocaine-prilocaine cream) (*Alster and Lupton 2002, Alster et al 2012, Bryan 2002, Chen et al 2003, Chen et al 2005, Doshi et al 2003, Jih et al 2004*).
- Lidocaine 5%
  - A randomized, double-blind, placebo-controlled, 2-period crossover trial (N = 32) evaluated patients with PHN who were regular users of lidocaine 5% plaster from open-label extension studies. Patients were assigned to receive 14 days of lidocaine 5% plaster followed by 14 days of placebo or vice versa with no washout period. The primary endpoint was the “time to exit” where patients withdrew because their pain relief was 2 points lower than their normal response on a 6-point categorical verbal rating scale of pain relief (worse, no pain relief, slight relief, moderate relief, a lot of relief, and complete relief). The median time to exit was 14 days for lidocaine 5% plaster and 3.8 days for placebo ($p < 0.001$) (*Galer et al 1999*). In patients with PHN, treatment with lidocaine resulted in significant pain relief compared to placebo (*Galer et al 1999*, *Galer et al 2002*, *Meier et al 2003*). In addition, treatment with lidocaine was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999*, *Meier et al 2003*).
  - The effectiveness of lidocaine patch 5% for the treatment of pain associated with PHN was demonstrated in a multi-center, open-label, phase 3 trial of up to 4 years duration. Patients applied up to 3 lidocaine 5% medicated plasters on the painful skin area for up to 12 hours a day. After 6 weeks, a mean pain relief of 4.3 ± 0.9 on a 6-point verbal-rating scale (1 = worse pain to 6 = complete relief) was reported and was maintained for the entire 12-month study and extension phase. The investigators' report for the global clinical impression of change was "very much improved" or "much improved" in about 80% of patients at each visit during the 12-month study. In the extension phase, the patient global impression of change was "very much" or "much" improved in 71% (49/69) at 24 months and 93% (40/43) at 36 months. In the safety population (n = 102) over the combined study period (4 years), drug-related adverse events included mainly administration site reactions: hypersensitivity (3.9%), pruritus (2.9%), irritation (2.9%), rash (2%), and skin reaction (1%) (*Sabatowski et al 2012*).
  - A Cochrane systematic review of 12 small studies (N = 508) assessed the analgesic efficacy of topical lidocaine (5% patch, 5% cream, 5% gel, and 8% spray) vs placebo or active control for chronic neuropathic pain in adults. The limited information from single studies, mainly in PHN, indicated that topical lidocaine may be effective in treating neuropathic pain in a small number of patients and is well tolerated, at least in the short-term. There was no clear evidence of an effect on the incidence of adverse effects or withdrawals. However, the reviewers noted that the studies included ‘very low quality evidence’ and all had a ‘high risk of bias’ due to small size and incomplete outcome data (*Derry et al 2014*).
  - In clinical studies, efficacy of the 5% lidocaine patch has consistently been reported to be superior to placebo and comparable or superior to oral pregabalin in patients with PHN pain or diabetic neuropathy (*Baron et al 2009a, Baron et al 2009b, Binder et al 2009, Rehm et al 2010, Rowbotham et al 1996*).
- Lidocaine topical system 1.8%
  - The approval of ZTlido (lidocaine topical system 1.8%) was based on trials that demonstrated the efficacy of *Lidoderm* for treatment of pain associated with PHN; no new clinical trials were required for FDA-approval (*The medical letter 2019*). In a single-dose, crossover study in 53 healthy volunteers, Ztlido 1.8% demonstrated equivalent exposure (area under the curve) and peak concentration of lidocaine to Lidoderm (*ZTlido prescribing information 2018*).

CLINICAL GUIDELINES

- Consensus guidelines for the use of topical anesthetics are lacking, therefore, decision making regarding the use of these agents is based on patient-specific factors and available comparative efficacy data.
  - The FDA recommends against using topical OTC medications for teething pain as some products may cause harm (*FDA Drug Safety* Communication *2018*).

- The American Academy of Pediatrics (AAP) recommends managing teething pain with a chilled (not frozen) teething ring or gently rubbing/massaging with the caregiver's finger. Use of topical anesthetics for teething is discouraged by the AAP and American Academy of Pediatric Dentistry (AAPD) (*AAPD 2012).*
- The 2010 European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain suggest topical lidocaine may be considered first-line if there are concerns of adverse events with other oral medications in elderly patients who have PHN (*Attal et al 2010*).

SAFETY SUMMARY

- **Contraindications**
  - Hypersensitivity to any component of the formulation; hypersensitivity to another local anesthetic of the amide type.
- **Warnings**
  - *All drugs in class*
    - Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use.
    - Overexposure: To avoid overexposure that could lead to adverse effects:
      - Do not use for longer duration or over larger surface areas than recommended.
      - Consider total amount of local anesthetics absorbed from all formulations.
      - Do not apply to mucous membranes or broken or inflamed skin.
      - Use with caution in patients who may be more sensitive to systemic effects, including acutely ill or debilitated patients, or those with severe hepatic disease or pseudocholinesterase deficiency.
    - Risk of secondary exposure to children and pets: store and dispose out of reach of children and pets due to the risk of accidental exposure and resulting toxicity.
    - Eye irritation: avoid contact with eyes
  - *Oral topical lidocaine viscous solution*
    - Boxed warning: Life-threatening and fatal events in infants and young children. There have been postmarketing cases of seizures, cardiopulmonary arrest, and death in patients < 3 years of age with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations. Lidocaine 2% viscous solution should generally not be used for teething pain. For other conditions, the use of lidocaine 2% viscous solution in patients < 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed. To decrease the risk of serious adverse events, caregivers should be instructed to strictly adhere to the prescribed dose and frequency of administration, and store the prescription bottle safely out of reach of children.
  - *Lidocaine patch and topical system*
    - The lidocaine patch is only recommended for use on intact skin.
    - Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patches is not recommended.
- **Key drug interactions**
  - Lidocaine and lidocaine-prilocaine cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.
- **Adverse events**
  - Lidocaine topical patch: application site reactions such as irritation, erythema, and pruritus.
  - Topical lidocaine and prilocaine: application site erythema (21% to 30%), application site pain, genital mucous membrane burning (17%).
  - Topical lidocaine and tetracaine: erythema (47%), skin discoloration (16%), and edema (14%).
  - Patients with severe hepatic impairment are at increased risk of developing lidocaine toxicity.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Doxepin	Cream 5%	Topical	Adults: apply a thin film 4 times/day. Not recommended for use over 8 days.	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Jelly 2%	Topical	Adults: No more than 30 mL (600 mg) in any 12-hour period according to the prescribing information	
lidocaine	Gel 2%, 3%, 4%	Topical	Apply to affected area ≤ 4 times daily as needed	
lidocaine	Lotion 3%, 3.5%, 4%	Topical	Apply a thin film to affected area 2 or 3 times daily	
lidocaine	Ointment 5%	Topical	Adults: A single application not exceeding 5 g of ointment; maximum: 20 g per day.	
lidocaine	Viscous solution 2%	Topical	Adults: 15 mL orally no more frequently than every 3 hours; 8 doses per 24 hours. Pediatrics: ≥ 3 years of age: recommendations vary by age and weight. < 3 years of age: ≤ 1.2 mL (maximum: 4 doses per 12-hour period; use only if the underlying condition requires treatment with product volume of ≤ 1.2 mL)	Not approved for relief of teething pain and discomfort in infants and children; serious adverse (toxic) effects have been reported. Max: 4.5 mg/kg/dose (or 300 mg/dose).
lidocaine	Solution 4%	Topical	Adults: 1 to 5 mL (40 to 200 mg) per dose when used as a spray, applied with cotton applicators or packs, as when instilled into a cavity; maximum dose: 4.5 mg/kg, not to exceed 300 mg per dose Pediatrics: Dose varies with age and weight (maximum dose: 4.5 mg/kg)	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Cream 2%, 3%, 3.25%, 3.88%, 4%, 4.12%	Topical	Apply a thin film to the affected area 2 to 4 times daily for skin irritation.	
lidocaine	Rectal cream 5%	topical	Apply to affected area up to 6 times daily	
lidocaine	Topical system 1.8% Patch 5%	Topical	Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Patches may be cut into smaller sizes with scissors prior to removal of the release liner
lidocaine-prilocaine	2.5-2.5% cream, 2.5-2.5% kit, 2.5-2.5% & 3.88% kit	Topical	Adults: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing.	Should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents.
lidocaine-prilocaine and lidocaine	lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	Topical	Cream: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing. Patch: Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Lidocaine and prilocaine cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents
Lidocaine-hydro-cortisone	2-2%, 3-0.5%, 3-1%, 3-2.5%, 2.8-0.55% kits	Topical	Twice daily or as directed.	
Lidocaine-tetracaine	Cream 7-7%	Topical	Apply 20 to 30 minutes before procedure.	See full prescribing information for amount according to treatment site.

(*Drug Facts & Comparison 2020, Lexicomp Online 2020*)

See the current prescribing information for full details.

CONCLUSION

- Many of the topical lidocaine and lidocaine/prilocaine products are available generically and are available in different formulations including cream, ointment, jelly, gel, and as a topical patch.
- Lidocaine produces its analgesics effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium.
- In general, adverse reactions associated with topical lidocaine are dose-related and may result from high plasma levels due to excessive dosage or rapid absorption, hypersensitivity, idiosyncrasy, or diminished tolerance. Common adverse reactions include localized skin reactions.
- Clinical evidence supporting the use of the lidocaine 5% patch in the treatment of PHN is limited due to the lack of comparative data to show clinical effectiveness.
  - A Cochrane review found no evidence from good quality randomized controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it is effective for relief of pain (*Derry et al 2014*).
- The evidence to support the use of lidocaine 5% patch for other types of pain is uncertain due to the lack of available evidence as the clinical trials that were conducted had small sample sizes and a short follow-up period, leading to a high risk of bias. However, EFNS guidelines suggest lidocaine patches can be considered first line for elderly patients with PHN at high risk for severe adverse effects with oral medications.

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Publication Date: April 1, 2020

Prior Authorization Guideline

Guideline Name Multiple Sclerosis (MS) Agents

1 . Indications

Drug Name: Zeposia (ozanimod)
Relapsing forms of MS Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 . Criteria

Product Name: Zeposia	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria	

1 - Diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses)

AND

2 - One of the following:

2.1 For continuation of therapy

OR

2.2 Failure after a trial of at least 4 weeks, contraindication, or intolerance to at least two of the following disease-modifying therapies for MS:

- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Tecfidera (dimethyl fumarate)

AND

3 - Prescribed by or in consultation with a neurologist

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

Approval Criteria

1 - Documentation of positive clinical response to therapy (e.g., improvement in radiologic disease activity, clinical relapses, disease progression)

AND

2 - Prescribed by or in consultation with a neurologist

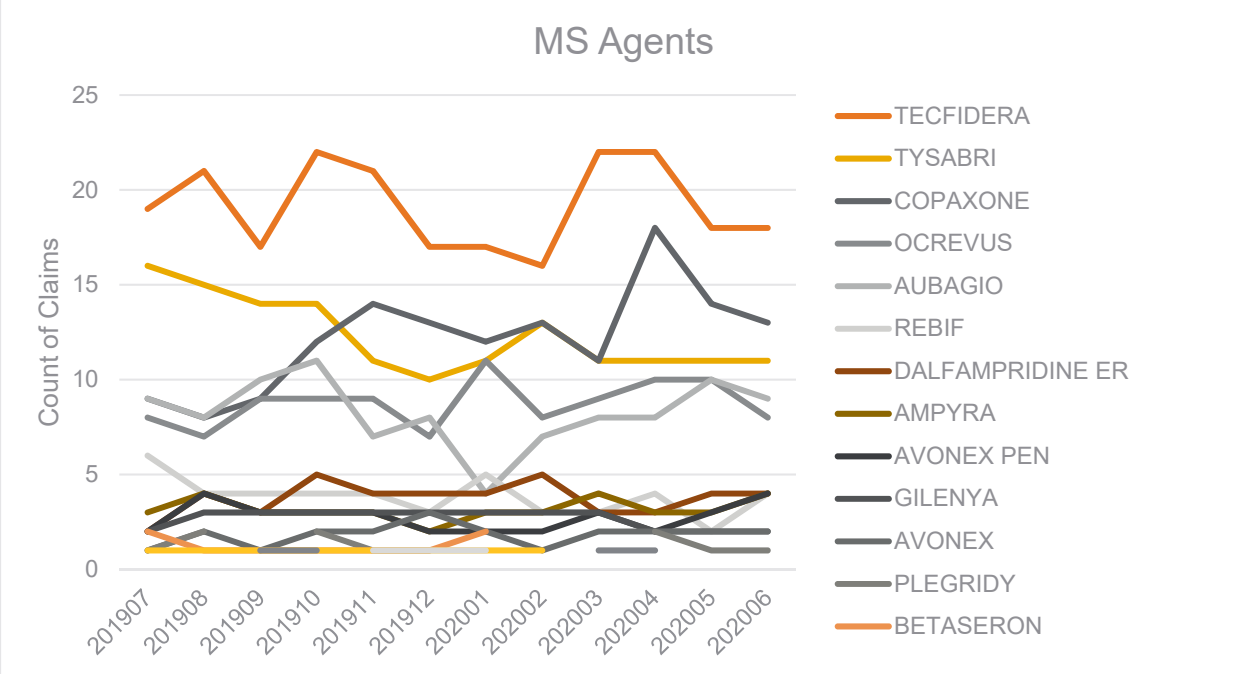
Nevada Medicaid

Multiple Sclerosis Agents

Fee for Service

July 1, 2019 – June 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
AMPYRA	5	38	1,140	2,280
AUBAGIO	18	99	2,956	2,986
AVONEX	3	22	616	22
AVONEX PEN	5	33	924	33
BETASERON	1	9	252	126
COPAXONE	16	146	4,168	2,472
DALFAMPRIDINE ER	8	45	1,350	2,700
GILENYA	3	32	960	960
GLATIRAMER ACETATE	2	8	234	96
GLATOPA	1	3	178	72
LEMTRADA	1	3	3	3.6
MAVENCLAD	1	1	28	9
MAYZENT	1	3	90	90
OCREVUS	60	105	1,616	1,750
PLEGRIDY	1	11	308	11
REBIF	5	46	1,218	276
REBIF REBIDOSE	2	4	112	24
TECFIDERA	34	230	6,896	13,792
TECFIDERA STARTER PACK	7	7	210	420
TYSABRI	23	148	1,166	2,220



CC. Multiple Sclerosis (MS) Agents

Therapeutic Class: Agents for the treatment of Neuromuscular Transmission Disorder
Last Reviewed by the DUR Board: January 23, 2020

MS Agents aresubject 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. Ampyria® (dalfampridine)

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

      1. The recipient must have a diagnosis of MS; and

      2. The medication is being used to improve the recipient's walking speed; and

      3. The medication is being prescribed by or in consultation with a neurologist; and

      4. The recipient is ambulatory and has an EDSS score between 2.5 and 6.5; and

      5. The recipient does not have moderate to severe renal dysfunction (CrCL >50 ml/min); and

      6. The recipient does not have a history of seizures; and

      7. The recipient is not currently pregnant or attempting to conceive.

   b. Prior Authorization Guidelines

      1. Initial prior authorization approval will be for three months.

      2. Request for continuation of therapy will be approved for one year.

2. Relapsing Forms of MS Agents:

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

      1. The recipient must have a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses).

   b. Lemtrada® (alemtuzumab)

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

a. The recipient must have a diagnosis of a relapsing form of MS; and one of the following:

1. Both the following:

a. The recipient has not been previously treated with alemtuzumab; and

b. The recipient has had failure after a trial of at least four weeks; a contraindication or intolerance to two of the following disease-modifying therapies for MS:

1. Aubagio (teriflunomide)

2. Avonex (interferon beta-1a)

3. Betaseron (interferon beta-1b)

4. Copaxone/Glatopa (glatiramer acetate)

5. Extavia (interferon beta-1b)

6. Gilenya (fingolimod)

7. Lemtrada (alemtuzumab

8. Mayzent (siponimod)

9. Ocrevus (ocrelizumab)

10. Plegridy (peginterferon beta-1a)

11. Rebif (interferon beta-1a)

12. Tecfidera (dimethyl fumarate)

13. Tysabri (natalizumab); or

2. Both the following:

a. The recipient has previously received treatment with alemtuzumab; and

b. The recipient has had at least 12 months elapsed or will have elapsed since the most recent treatment course with alemtuzumab; and

3. The medication will not be used in combination with another disease-modifying therapy for MS.

2. Prior Authorization Guidelines

a. Initial authorization approval will be for 12 months.

b. Recertification approval will be for 12 months.

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

c. Mavenclad® (cladribine)

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

a. The recipient must have a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses); and one of the following:

1. Both the following:

a. The recipient has not been previously treated with cladribine; and

b. The recipient has had failure after a trial of at least four weeks; contraindication, or intolerance to two of the following disease-modifying therapies for MS:

1. Aubagio (teriflunomide

2. Avonex (interferon beta-1a)

3. Betaseron (interferon beta-1b)

4. Copaxone/Glatopa (glatiramer acetate)

5. Extavia (interferon beta-1b)

6. Gilenya (fingolimod)

7. Lemtrada (alemtuzumab)

8. Mayzent (siponimod)

9. Ocrevus (ocrelizumab)

10. Plegridy (peginterferon beta-1a)

11. Rebif (interferon beta-1a)

12. Tecfidera (dimethyl fumarate)

13. Tysabri (natalizumab); or

2. Both the following:

a. The recipient has previously received treatment with cladribine; and

b. The recipient has not already received the FDA-recommended lifetime limit of two treatment courses (or four treatment cycles total) of cladribine; and

b. The medication will not be used in combination with another disease-modifying therapy for MS.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one month.

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

d. Ocrevus® (ocrelizumab)

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

a. The recipient has a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses); and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

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

a. Documentation of a positive clinical response to Ocrevus® therapy; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

3. Prior Authorization Guidelines

a. Initial prior authorization approval will be 12 months.

b. Recertification approval will be for 12 months.

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

3. Primary Progressive Forms of Multiple Sclerosis (PPMS) Agents:

a. Ocrevus® (ocrelizumab)

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

a. The recipient must have a diagnosis of PPMS; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

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

a. Documentation of a positive clinical response to Ocrevus® therapy; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell target therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

3. Prior Authorization Guidelines

a. Initial prior authorization approval will be for 12 months.

b. Recertification approval will be for 12 months.

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

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is among the most common causes of neurological disability in young adults *(MS Coalition 2019; National Institutes of Health MS 2019)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes. Most patients with MS experience relapses and remissions of neurological symptoms, usually early in the disease process, with clinical events that are generally associated with CNS inflammation. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for an estimated 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 15% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. Patients who experience a CIS may or may not develop MS *(Sanvito et al 2011, National MS Society 2020[a])*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the historical category of progressive-relapsing multiples sclerosis (PRMS) can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States are affected by MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is at least 2 to 3 times more common in women than in men *(National MS Society 2020[b])*.
- Diagnosis of MS requires evidence that demonstrates lesions in the CNS showing “dissemination in space” (ie, suggestions of damage in > 1 place in the nervous system) and “dissemination in time” (ie, suggestions that damage has occurred more than once). It is a diagnosis of exclusion, after consideration of and elimination of more likely diagnoses *(Thompson et al 2018)*.
- The patient evaluation includes an extensive history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that lead to damage to the myelin and slowing or blocking of transmission of nerve impulses. A true MS exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of disease-modifying therapies (DMTs) to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018)*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guidelines recommend initiation of DMTs early on in the patient’s disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*.The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients’ clinical response and tolerability to medications should be monitored (*MS Coalition 2019, Rae-Grant et al 2018, Scolding et al 2015*).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing-remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2020*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- A recently approved agent in this review, Vumerity (diroximel fumarate), is rapidly converted to monomethyl fumarate (MMF), which also is the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved gastrointestinal (GI) tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019*). In April 2020, the FDA approved another agent in this class, Bafiertam (monomethyl fumarate). This drug is considered a "bioequivalent alternative" to dimethyl fumarate since dimethyl fumarate is a prodrug, and monomethyl fumarate is its active ingredient. Since the drug is already in its active form, it is administered at a lower dose than dimethyl fumarate, and it is thought that it may lead to fewer GI adverse effects (*Drugs@FDA 2020*).

- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review[§]

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Bafiertam (monomethyl fumarate)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa[†] (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	✔ *
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)	-
Mayzent (siponimod)	-
mitoxantrone[‡]	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-
Zeposia (ozanimod)	-

*Generics have received FDA-approval; however, settlement agreements will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, the manufacturer has voluntarily withdrawn Zinbryta (daclizumab) from the market; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta.

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

INDICATIONS

- In 2019, the FDA requested all manufacturers of drugs indicated for treatment of MS to revise the language of the indications to conform to contemporary nomenclature. As of May 22, 2020, all drugs have received revised FDA-approved indications except mitoxantrone (*Drugs@FDA 2020*).

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS
Ampyra (dalfampridine)	✔ *	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-
Copaxone (glatiramer acetate)	-	✔	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-
Lemtrada (alemtuzumab)	-	-	✔ ‡ (3rd line)	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-
Mayzent (siponimod)	-	✔	-	-	-
mitoxantrone	-	-	-	-	✔ ‖
Ocrevus (ocrelizumab)	-	✔	-	✔	-
Plegridy (peginterferon β-1a)	-	✔	-	-	-
Rebif (interferon β-1a)	-	✔	-	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-
Tysabri (natalizumab)	-	✔ ¶	-	-	-
Vumerity (diroximel fumarate)	-	✔	-	-	-
Zeposia (ozanimod)	-	✔	-	-	-

*Ampyra is indicated as a treatment to improve walking in adult patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. Lemtrada is not recommended for use in patients with CIS because of its safety profile.
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.

‖Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications including pain related to advanced hormone-refractory prostate cancer and initial therapy of acute nonlymphocytic leukemia (includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias).
¶Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF- α.

(Prescribing information: Ampyra 2019, Aubagio 2020, Avonex 2020, Bafiertam 2020, Betaseron 2019, Copaxone 2020, Extavia 2019, Gilenya 2019, Glatopa 2019, Lemtrada 2020, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Ocrevus 2020, Plegridy 2020, Rebif 2019, Tecfidera 2020, Tysabri 2020, Vumerity 2020, Zeposia 2020)

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

CLINICAL EFFICACY SUMMARY

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biological response modifiers in reducing the frequency of relapses, lesions on MRI scans, and possibly delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons (IFNs) and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al 1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. Results from several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to Rebif (IFNβ-1a SC 3 times weekly) or Betaseron (IFNβ-1b every other day) or glatiramer acetate *(Barbero et al 2006, Durelli et al 2002, Khan et al 2001[a], Khan et al 2001[b], Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002). While a MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased

radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001).

- In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another recommended therapy is safe and effective *(Caon et al 2006, Carra et al 2008, Zwibel 2006,)*. Patients switching to glatiramer acetate after experiencing an inadequate response to IFNβ-1a therapy had a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (n = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, randomized, placebo-controlled trial. Eligible adult patients had RRMS with a baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.

- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the "placebo-switch group"). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different from the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weighted hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.
- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse was reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly (p < 0.001 for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both p < 0.0001) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; p < 0.001). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions on MRI. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%, respectively).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio (teriflunomide) were evaluated in two Phase 3, double-blind, placebo-controlled, RCTs – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.

- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif (IFNβ-1a SC) were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in 1237 patients with RRMS over 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Bafiertam (monomethyl fumarate)

- The efficacy of monomethyl fumarate, the active moiety of dimethyl fumarate, is based on bioavailability studies in healthy patients comparing oral dimethyl fumarate delayed-release capsules to monomethyl fumarate delayed-release capsules. Analyses compared the blood levels of monomethyl fumarate to establish bioequivalency and support the FDA approval (*Bafiertam Prescribing Information 2020*).

Tysabri (natalizumab)

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

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two Phase 3, open-label RCTs in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.

- Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
- The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
- In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
- In the CARE-MS II trial, alemtuzumab significantly reduced the relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
- Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
- During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year of the extension study *(Garnock-Jones 2014)*.

- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2-weighted lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017, Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a 44 mcg SC 3 times weekly) in 1656 patients with relapsing MS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFNβ-1a SC) across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
      - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).

        - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; p < 0.001)
        - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; p < 0.001)
    - The most common adverse events were infusion-related reactions and infections.
- No opportunistic infections, including PML, were reported in any group over the duration of either trial.
    - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
    - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
        - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
- ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
    - The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*).
    - For the primary endpoint, the percentages of patients with 12-week confirmed disability progression were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; p = 0.03).
    - The percentages of patients with 24-week CDP, a secondary endpoint, were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; p = 0.04).
    - Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
        - The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
        - From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001).
        - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02).
    - Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
    - Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
        - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Mayzent (siponimod)

- The Phase 3 EXPAND trial was a double-blind, parallel-group, placebo-controlled, time-to-event RCT in patients with SPMS who had evidence of disability progression in the previous 2 years (*Kappos et al 2018*).
    - A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546).
    - A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study.
        - The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.

- For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR 0.79; 95% CI: 0.65 to 0.95; RR reduction, 21%; p = 0.013).
- Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25FW) and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW.
- Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal p < 0.01). The absolute reduction in the ARR was 0.089 with siponimod.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter RCT to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study reenrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR:
    - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each p < 0.001).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks in both cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each p < 0.001 vs placebo).
  - Cladribine 3.5 mg/kg significantly lowered the ARR vs the 5.25 mg/kg treatment group.

Vumerity (diroximel fumarate)

- The efficacy of diroximel fumarate was established through bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate to diroximel fumarate (*Vumerity Prescribing Information 2020*).
- In a Phase 3, open-label, long-term safety study, 696 patients with RRMS (EVOLVE-MS-1) were administered diroximel fumarate 462 mg twice daily for up to 96 weeks (*Palte et al 2019*). Interim results revealed that GI treatment-emergent adverse events occurred in 215 (30.9%) of patients; the vast majority of these events (207 [96%]) were mild or moderate in severity. Gastrointestinal events occurred early in therapy, resolved (88.8%; 191/215), and were of short duration (median 7.5 days) in most patients. Discontinuation of treatment due to a GI treatment-emergent adverse event occurred in < 1% of patients.
- Topline results from the randomized, double-blind, 5-week, Phase 3, EVOLVE-MS-2 study also demonstrated significantly improved GI tolerability with diroximel fumarate vs dimethyl fumarate in 506 patients with RRMS (*Selmaj et al 2019*). Patients were randomized to diroximel fumarate 462 mg twice daily or dimethyl fumarate 240 mg twice daily. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) rating scale. Results revealed that patients treated with diroximel fumarate self-reported significantly fewer days of key GI symptoms with intensity scores ≥ 2 as compared to dimethyl fumarate (p = 0.0003). The most commonly reported adverse events for both groups were flushing, diarrhea, and nausea.

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were compared to Avonex (IFNβ-1a IM) in two multicenter, Phase 3, double-blind, double-dummy RCTs in patients with relapsing forms of MS– SUNBEAM and RADIANCE (*Comi et al 2019, Cohen et al 2019)*. In the studies, which were conducted over a minimum of 12 months, patients were randomized 1:1:1 to oral ozanimod 0.5 mg daily, oral ozanimod 1 mg daily, or Avonex (IFNβ-1a) 30 mcg IM once weekly. Patients randomized to ozanimod received a placebo IM injection once weekly, and those randomized to IFN received placebo capsules once daily.
  - All patients received an initial 7-day dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Prophylactic administration of acetaminophen or ibuprofen was recommended 1 hour before each IFN or placebo injection and every 6 hours for 24 hours after the injection.
  - Patients in both trials (n = 1346 for SUNBEAM and n = 1320 for RADIANCE) had an EDSS score of ≤ 5, and a history of at least 1 relapse within 12 months prior to screening or 1 relapse within 24 months in addition to at least 1 Gd-enhancing lesion within 12 months prior to screening. The primary endpoint in both trials was the ARR.

- In the SUNBEAM, the ARR was 0.18 (95% CI: 0.14 to 0.24) for ozanimod 1 mg, 0.24 (95% CI: 0.19 to 0.31) for ozanimod 0.5 mg, and 0.35 (95% CI: 0.28 to 0.44) for IFNβ-1a. Significant reductions in ARR were observed compared to IFNβ-1a with both ozanimod 1 mg (rate ratio, 0.52; 95% CI: 0.41 to 0.66; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.69; 95% CI: 0.55 to 0.86; p = 0.0013).
- In the RADIANCE trial, adjusted ARRs were found to be 0.17 (95% CI: 0.14 to 0.21) for ozanimod 1 mg, 0.22 (95% CI: 0.18 to 0.26) for ozanimod 0.5 mg, and 0.28 (95% CI: 0.23 to 0.32) for IFNβ-1a. The rate ratios were significant when comparing ozanimod 1 mg (rate ratio, 0.62; 95% CI: 0.51 to 0.77; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.79; 95% CI: 0.65 to 0.96; p = 0.0167) to IFNβ-1a.
- Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Symptomatic MS

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

Clinically Isolated Syndrome (CIS)

- IFNs, Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
  - In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2-year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
  - A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
  - A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to CDMS in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient

information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
  - The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and PRMS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd-enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data, including cohort data, for mitoxantrone. An evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.
- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. Results from the ASCEND trial, evaluating natalizumab in SPMS, found no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patients with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on a low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- A total of 39 RCTs evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - fingolimod: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - fingolimod: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
    - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
    - alemtuzumab: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
    - natalizumab: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
  - Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR = 2.24, 95% CI: 1.5 to 3.34); peginterferon beta-1a (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and fingolimod (RR = 8.26, 95% CI: 3.25 to 20.97).
  - Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
    - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
    - natalizumab: RR = 1.53, 95% CI: 0.93 to 2.53
    - alemtuzumab: RR = 0.72, 95% CI: 0.32 to 1.61
- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).

- Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
- Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
- The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.

- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N = 16,998) (*CADTH 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and fingolimod (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI: 0.62 to 0.93) compared with glatiramer acetate.
  - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for natalizumab to 0.74 (95% CI: 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
  - Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
  - Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
  - The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.
- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.

- Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
- No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
- None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.

- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR = 0.69, 95% CI: 0.55 to 0.87).

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT in women of childbearing potential who have MS. (Level B)
    - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
    - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
    - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
    - Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
    - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
  - Switching DMTs
    - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
    - Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
    - Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
    - Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching

DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
    - Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
    - Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
    - Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
    - Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
    - Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)
  - Stopping DMTs
    - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)
- In September 2019, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS *(MS Coalition 2019)*. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing MS, regardless of the person's age. Relapsing MS includes CIS, RRMS, and active SPMS with clinical relapses or inflammatory activity on MRI.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly diagnosed individuals with highly active MS.
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents.
  - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
    - Suboptimal treatment response as determined by the individual and his or her treating clinician
    - Intolerable side effects
    - Inadequate adherence to the treatment regimen
    - Availability of a more appropriate treatment option

        - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
    - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
    - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
    - The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the patient and his/her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.
    - Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
        - MS clinical phenotypes may respond differently to different DMTs.
        - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
        - Potential contraindications limit options for some individuals.
        - Risk tolerance varies among people with MS and their treating clinicians.
        - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
        - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
        - Pregnancy and breastfeeding limit the available options.
    - Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
    - Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
- Treatment should not be withheld during determination of coverage by payors as this puts the patient at risk for recurrent disease activity. The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*). The main recommendations reported were the following:
    - The entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive patient assessment, detection of adverse effects, and the capacity to address adverse effects properly if they occur. (Consensus statement)
    - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
    - Offer early treatment with DMTs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
    - For active RRMS, choosing among the wide range of available drugs from the modestly to highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
    - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile. (Weak)
    - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
    - Consider ocrelizumab for patients with active SPMS. (Weak)
    - Consider ocrelizumab for patients with PPMS. (Weak)
    - Always consult the summary of product characteristics for dosage, special warnings, precautions, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
    - Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
    - When monitoring treatment response in patients treated with DMTs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
    - When monitoring treatment response in patients treated with DMTs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)

- When monitoring treatment safety in patients treated with DMTs, perform a standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
- Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
- Consider continuing a DMT if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
- Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses, and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including peginterferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, anaphylaxis, congestive heart failure (CHF), potential development of autoimmune disorders (eg, lupus erythematosus), and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) are associated with influenza-like symptoms including musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, or urticaria immediately following the injection. Injection site reactions including lipoatrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during Gilenya

treatment initiation. In controlled clinical trials, first-degree AV block after the first dose occurred in 4.7% of patients receiving Gilenya and 1.6% of patients on placebo.

- Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination of the drug may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with an active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with fingolimod; HPV infections including papilloma, dysplasia, warts, and HPV-related cancer have been reported in post marketing reports. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, and lymphoma in patients treated with fingolimod. Clinically significant hepatic injury has occurred in patients treated with fingolimod in the postmarketing setting; hepatic function should be monitored prior to, during, and until 2 months after medication discontinuation. Cases of PML have occurred in the postmarketing setting, primarily in patients who were treated with fingolimod for at least 2 years. At the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports. Relapses of MS with tumefactive demyelinating lesions on imaging have been observed both during therapy with fingolimod and after discontinuation in post marketing reports. If a severe MS relapse occurs during or after discontinuation of treatment with fingolimod, tumefactive MS should be considered, and imaging evaluation and initiation of appropriate treatment may be necessary.

- Teriflunomide is contraindicated in patients with severe hepatic impairment; pregnancy, those with a history of hypersensitivity to the medication, women of childbearing potential who are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include bone marrow effects, immunosuppression leading to potential infections, malignancy risk, interstitial lung disease, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels more rapidly. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate, diroximel fumarate, and monomethyl fumarate are contraindicated in patients with hypersensitivity to the products or any of their excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury. Serious cases of herpes zoster and other opportunistic viral (eg, herpes simplex virus, West Nile virus, cytomegalovirus), fungal (eg, Candida and Aspergillus), and bacterial (eg, Nocardia, Listeria monocytogenes, *Mycobacterium tuberculosis*) infections have been reported in patients treated with dimethyl fumarate, and may occur at any time during treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate. Patients with signs/symptoms of any of these infections should undergo diagnostic evaluation and receive appropriate treatment; treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate may need to be withheld until the infection has resolved. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or a temporary dose reduction may reduce flushing. Diroximel fumarate should not be coadministered with dimethyl fumarate.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10% in MS) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include

hypersensitivity reactions, increased risk of herpes encephalitis and meningitis, increased risk of infections (including opportunistic infections), and hepatotoxicity.

- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure, potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia, autoimmune hepatitis, and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies (ie, thyroid cancer, melanoma, and lymphoproliferative disorders/lymphoma). Alemtuzumab is only available through a restricted distribution and REMS program, which requires the member, provider, pharmacy, and infusion facility to be certified. Approximately one-third of patients who received alemtuzumab in clinical trials developed thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Other safety concerns within the product labeling include a warning that patients administered alemtuzumab are at risk for serious infections, including those caused by *Listeria monocytogenes,* the potential development of pneumonitis, and PML. Patients that are prescribed alemtuzumab should be counseled to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should also undergo tuberculosis screening according to local guidelines. With regard to PML, alemtuzumab should be withheld, and appropriate diagnostic evaluations performed, at the initial occurrence of suggestive signs or symptoms.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with relapsing MS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with relapsing MS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
  - Live or live-attenuated vaccines should not be administered until B-cell count recovery is confirmed (as measured by CD19+ B-cells) in infants born from mothers who were exposed to ocrelizumab during pregnancy.

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine may cause seizures; permanently discontinue this medication in patients who have a seizure while on treatment. Dalfampridine can also cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as an adverse reaction in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Mayzent may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most common adverse events (incidence > 10%) are headache, hypertension, and transaminase increases.
- Ozanimod is contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. It is also contraindicated in patients with Mobitz type II second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Use is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod due to fetal risk. The most common adverse events (incidence > 10%) are upper respiratory tract infections and hepatic transaminase elevations. Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod and siponimod.
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				severe renal impairment (CrCl ≤ 50 mL/min). There are no adequate and well-controlled studies of dalfampridine in pregnant women; use during pregnancy only if the benefit justifies the potential fetal risk.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection; pen, prefilled syringe	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Bafiertam (monomethyl fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 95 mg twice daily for 7 days (initiation), then 190 mg twice daily (maintenance) Temporary dose reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to monomethyl fumarate; studies did not show that the presence of food had an impact on the incidence of flushing with monomethyl fumarate. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤40 kg, a lower dose is recommended. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if HR < 45 bpm in adults, < 55 bpm in pediatric patients ≥ 12 years of age, or < 60 bpm in pediatric patients 10 or 11 years of age, new onset second degree or

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				higher AV block, or if the lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with continuous ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with a known risk of torsades de pointes or drugs that slow heart rate or AV conduction. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment. Fingolimod may cause fetal harm when administered to a pregnant woman. Before initiation of treatment with fingolimod, females of reproductive potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment and for 2 months after treatment to allow the compound to be eliminated from the body. In females planning to become pregnant, fingolimod should be stopped 2

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				months before planned conception.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatment courses. Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter); serum transaminases and total bilirubin (prior to treatment initiation and periodically thereafter) Measure the urine protein to creatinine ratio prior to treatment initiation Conduct baseline and yearly skin exams to monitor for melanoma.	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is	The use of Mavenclad in patients weighing less than 40 kg has not been investigated. Mavenclad is contraindicated in pregnant women and in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			divided into 2 treatment cycles: • First course/first cycle: start anytime • First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	female/males of reproductive potential that do not plan to use effective contraception. Follow standard cancer screening guidelines because of the risk of malignancies. Administer all immunizations according to guidelines prior to treatment initiation. Obtain a complete blood count with differential including lymphocyte count. Lymphocytes must be within normal limits before treatment initiation and at least 800 cells/microliter before starting the second treatment course.
Mayzent (siponimod)	Tablets	Oral	Once daily Initiate treatment with a 5-day titration; a starter pack should be used for patients who will be titrated to the maintenance dosage starting on Day 6 (refer to prescribing information for titration regimen).	Mayzent can cause fetal harm when administered to pregnant women. Dosage should be titrated based on patient's CYP2C9 genotype. Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of CHF develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥ 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 $cells/mm^3$.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			course of mitoxantrone and in the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 2 (non-live vaccines) to 4 (live or live-attenuated vaccines) weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe	SC	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a); Rebif Rebidose	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance) Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	Must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. Avoid administration with a high-fat, high-calorie meal/snack. Avoid co-administration with alcohol. The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to diroximel fumarate. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with diroximel fumarate.
Zeposia (ozanimod)	Capsules	Oral	Once daily Titration: 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7, then 0.92 mg once daily on day 8 and thereafter.	May be taken with or without food. Capsules should be swallowed whole. Obtain a complete blood count (including lymphocyte count), transaminase and bilirubin levels, electrocardiogram, and ophthalmic assessment before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				If a dose is missed during the first 2 weeks of treatment, treatment should be restarted using the titration regimen; if a dose is missed after 2 weeks of treatment, continue treatment as planned. Use in patients with hepatic impairment is not recommended.

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

CONCLUSION

- DMTs for MS have shown benefits in patients with relapsing MS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite relapsing MS begin DMTs *(MS Coalition 2019)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2019)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with low dose IM IFNβ-1a compared to higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products. With IFNβ, use caution in patients with depression or other mood disorders. The adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. The premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure with another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 8 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved in 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Mavenclad (cladribine), Mayzent (siponimod), and Vumerity (diroximel fumarate) were all approved in 2019; Zeposia (ozanimod) and Bafiertam (monomethyl fumarate) were approved in 2020. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and/or tolerability profiles. The efficacy of the oral products has not been directly compared in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability

progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
    - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
- Zeposia (ozanimod) is another sphingosine 1-phosphate receptor modulator that was approved by the FDA in March 2020. Clinical trials have shown ozanimod to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class it does not require first dose cardiac monitoring (*Comi 2019, Cohen 2019*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Vumerity (diroximel fumarate) is a recently approved oral agent for MS and is rapidly converted to monomethyl fumarate, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019).*
- Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a “bioequivalent alternative” to dimethyl fumarate (*Drugs@FDA 2020*).
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O’Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.
- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
    - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years (RR, 0.74, 95% CI: 0.62 to 0.89) *(Pucci et al 2011)*. Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.

- Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of relapsing MS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.

- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS (*MS Coalition 2019*).
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents (*MS Coalition 2019*).

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Publication Date: June 22, 2020

Prior Authorization Guideline

Guideline Name GNRH/LHRH Antagonists and Combinations

1 . Indications

Drug Name: Orilissa (elagolix)
Endometriosis Indicated for the management of moderate to severe pain associated with endometriosis.
Drug Name: Oriahnn (elagolix, Estradiol, and Norethindrone)
Heavy menstrual bleeding: Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

2 . Criteria

Product Name: Orilissa 150 mg	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of moderate to severe pain associated with endometriosis

AND

2 - One of the following: [2, 3]

2.1 History of inadequate pain control response following a trial of at least 3 months, or history of intolerance or contraindication to one of the following:

- Danazol
- Combination (estrogen/progesterone) oral contraceptive
- Progestins

OR

2.2 Patient has had surgical ablation to prevent recurrence

Product Name: Orilissa 150 mg	
Approval Length	6 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has improvement in pain associated with endometriosis (e.g., improvement in dysmenorrhea and nonmenstrual pelvic pain)

AND

2 - Treatment duration of Orilissa has not exceeded a total of 24 months [1]

Product Name: Orilissa 200 mg*	
Approval Length	6 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of moderate to severe pain associated with endometriosis

AND

2 - One of the following: [2, 3]

2.1 History of inadequate pain control response following a trial of at least 3 months, or history of intolerance or contraindication to one of the following:

- Danazol
- Combination (estrogen/progesterone) oral contraceptive
- Progestins

OR

2.2 Patient has had surgical ablation to prevent recurrence

Notes	*NOTE: Orilissa 200 mg is used for a maximum of 6 months.

Product Name: Oriahnn Cap	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids)

AND

2 - One of the following:

2.1 History of inadequate response following a trial of at least 3 months, or history of intolerance or contraindication to one of the following:

- Combination (estrogen/progesterone) oral contraceptive
- Progestins
- Intrauterine contraception

OR

2.2 Patient has had surgical ablation to prevent recurrence

Product Name: Oriahnn Cap

Approval Length	6 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has improvement in menstrual bleeding.

AND

2 - Treatment duration of Oriahnn has not exceeded a total of 24 months [1]

3 . References

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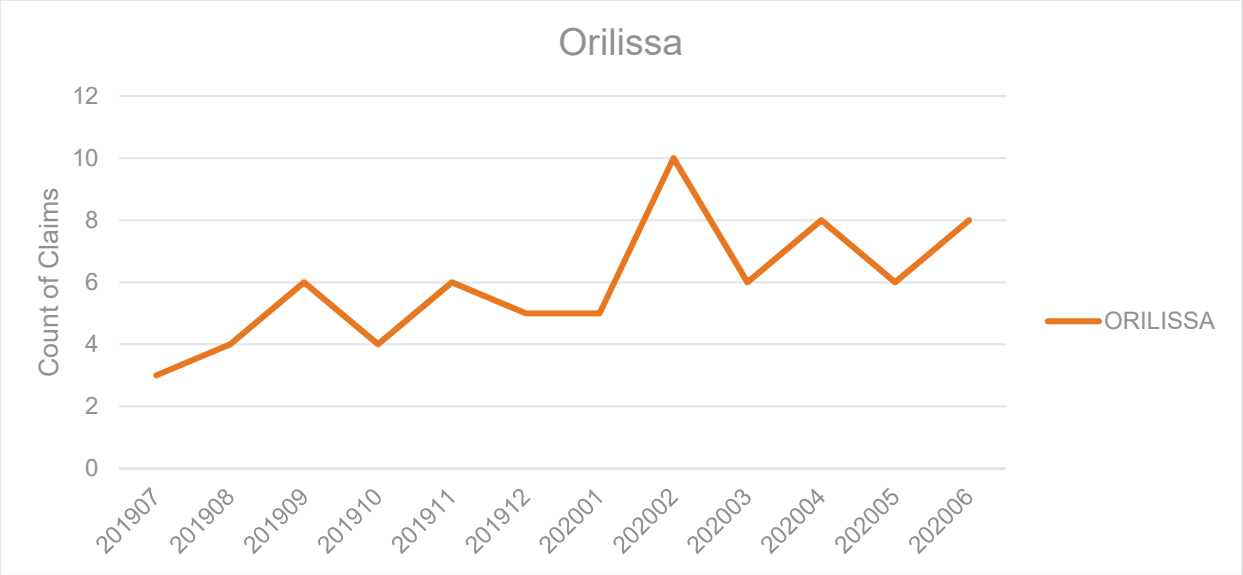
Nevada Medicaid

GNRH/LHRH Antagonists and Combinations

Fee for Service

July 1, 2019 – June 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
ORILISSA	19	71	2,496	2,828



INTRODUCTION

Central Precocious Puberty (CPP)

- Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function *(Britto et al 2016)*. Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors *(Macedo et al 2014).*
  - While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls and 9 to 9.5 years in boys for the lower limit of normal pubertal development *(Carel et al 2004)*.
- CPP is characterized by the early onset of pubertal manifestations in girls and boys *(Carel et al 2004)*.
  - CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion *(Carel and Léger 2008).*
  - These manifestations consist primarily of breast development in girls and testicular enlargement in boys *(Carel and Léger 2008)*.
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion and finally suppression of the release of gonadal sex hormones *(Fuqua 2013, Klein et al 2016).*
  - There are several GnRH agonists available in varying doses and formulations. Depot formulations are generally preferred due to improved compliance *(Guaraldi et al 2016).* GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:
    - Lupron Depot-Ped (leuprolide), available as monthly or every 3 month intramuscular (IM) injections.
    - Synarel (nafarelin) intranasal spray, a short-acting spray that requires multiple inhalations daily.
    - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks. Of note, Trelstar (triptorelin pamoate) IM injection was the first FDA-approved triptorelin formulation; it was used off-label to treat CPP until Triptodur was made available in 2017 *(Klein et al 2016)*.
  - The optimal time to discontinue a GnRH agonist has not been established, but retrospective analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes *(Carel and Léger 2008).*

Endometriosis

- Endometriosis is a chronic, estrogen-dependent disorder characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity *(Brown and Farquhar 2015, Giudice 2010, Schenken 2018).*
  - Endometriosis affects 6% to 10% of women of reproductive age; it is present in approximately 38% of women with infertility and in up to 87% of women with chronic pelvic pain (*Armstrong 2010).*
  - The clinical presentation of endometriosis is highly variable and ranges from debilitating non-menstrual pelvic pain (NMPP) to infertility to no symptoms. Patients can present with dysmenorrhea, abdominal or pelvic pain, dyspareunia, and infertility *(Schrager et al 2013).*
- Although several pharmacological options are available for the treatment of endometriosis, none provide a cure, long-term relief of symptoms, or resolution of infertility.
  - GnRH agonists, such as Zoladex 3.6 mg (goserelin), Lupaneta Pack (leuprolide acetate/norethindrone), Lupron Depot 3.75 mg or Lupron Depot 11.25 mg 3-month injection (leuprolide), and Synarel (nafarelin) are recommended as second-line pharmacologic therapy after non-steroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives *(American College of Obstetricians and Gynecologists [ACOG] 2010, Armstrong 2010, American Society for Reproductive Medicine [ASRM] 2014).*
    - GnRH agonists are generally not recommended as a long-term therapy, due to the potential for dose and duration-dependent bone loss *(ACOG 2010).*
  - Orilissa (elagolix), the first and only available oral GnRH antagonist, was FDA-approved in July 2018 for the management of moderate to severe pain associated with endometriosis.

- Elagolix exerts its effect by rapidly suppressing the pituitary ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression.
- Similar to GnRH agonists, elagolix is indicated for short-term use, ie, 6 months for patients taking 200 mg orally twice daily (for coexisting dyspareunia) and 24 months for patients taking 150 mg orally daily.
- Other GnRH antagonists, such as Cetrotide (cetrorelix), Firmagon (degarelix), and ganirelix are only available as an injectable formulation; however, these agents are not FDA-approved for the treatment of endometriosis.

Uterine fibroids

- Uterine fibroids, also known as uterine leiomyomas or myomas, are monoclonal tumors that arise from the uterine smooth-muscle tissue *(Sohn et al 2018).*
  - It is estimated that 60% of women of reproductive age are affected, and 80% of women develop the disease during their lifetime.
  - Heavy or prolonged menstrual bleeding, abnormal uterine bleeding, resultant anemia, pelvic pain, infertility, and/or recurrent pregnancy loss are generally associated with uterine fibroids.
  - The majority of women with uterine fibroids either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the number, size, and/or location of fibroids are critical determinants of its clinical manifestations.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata *(Sohn et al 2018).*
  - Lupron Depot 3.75 mg is administered concomitantly with iron therapy. The clinician may wish to consider a 1-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate.

Infertility

- Infertility is typically defined as the inability to achieve pregnancy after 1 year of unprotected sexual intercourse *(Anwar and Anwar 2016).*
  - Infertility is common with a prevalence estimated at 9 to 18% *(Hanson et al 2017).*
  - Patients who are struggling to conceive report feelings of depression, anxiety, isolation, and loss of control *(Rooney and Domar 2018).*
  - An estimated 50% of infertility cases among heterosexual couples are attributable to female factors, 20% to male factors, and 30% to combined female and male factors or unknown factors (*Centers for Disease Control [CDC] 2018*, *Fauser 2018, Shreffler et al 2017*).
    - The most common causes of female infertility include ovulatory disorders (most commonly due to polycystic ovary syndrome [PCOS]), endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia.
    - The most common causes of male infertility are low concentrations, poor motility, and abnormal morphology of sperm.
- Pharmacologic agents used in anovulatory women to induce or control ovulation include clomiphene (the most widely used fertility treatment), letrozole (off-label indication), gonadotropins (FSH products and human chorionic gonadotropin [hCG] products), and GnRH antagonists (cetrorelix and ganirelix). Other pharmacological agents used include metformin (in PCOS patients) and dopamine agonists (for hyperprolactinemic anovulation) *(Seli and Arici 2018).*
  - GnRH antagonists, such as cetrorelix and ganirelix, are used in conjunction with assisted reproductive technology (ART), which is defined as any fertility treatment in which either eggs or embryos are handled. The 2 most common ART procedures utilized in the U.S. are in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) *(CDC 2018).*
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists; Gonadotropin Releasing Hormone Antagonist

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetrotide (cetrorelix) 0.25 mg injection	-
ganirelix 250 mcg injection	✔

Drug	Generic Availability
Lupaneta Pack (leuprolide acetate 3.75 mg depot suspension; norethindrone acetate 5 mg tablets and leuprolide acetate 11.25 mg depot suspension; norethindrone acetate 5 mg tablets)	-
Lupron Depot-Ped (leuprolide acetate for depot suspension) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25 mg, 30 mg (3-month)	-
Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (monthly), 11.25 mg (3-month)	-
Orilissa (elagolix) 150 mg, 200 mg tablets	-
Supprelin LA (histrelin) 50 mg implant	-
Synarel (nafarelin) nasal spray	-
Triptodur (triptorelin) 22.5 mg extended-release suspension	-
Zoladex (goserelin) 3.6 mg implant	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cetrotide (cetrorelix)	ganirelix	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Orilissa (elagolix)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) implant
Treatment of children with CPP					✔		✔	✔	✔	
Management of endometriosis, including pain relief and reduction of endometriotic lesions				✔				✔		✔
Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding										✔
Initial management of the painful symptoms of endometriosis			✔	✔ †						
Management of recurrence of endometriosis symptoms			✔	✔ †						
Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata				✔ ‡						
Management of moderate to severe pain associated with endometriosis						✔				
Inhibition of premature LH surges in women undergoing controlled ovarian stimulation*	✔	✔								

Abbreviations: CPP = central precocious puberty; LH = luteinizing hormone

*The word “stimulation” is used in the cetrorelix indication, while the word “hyperstimulation” is used in the ganirelix indication.

† In combination with norethindrone acetate 5 mg tablet taken once daily

‡ Concomitantly with iron therapy

(*Prescribing information: Cetrotide 2018, ganirelix 2018, Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 2018, Orilissa 2018, Supprelin LA 2017, Synarel 2017, Triptodur 2018, Zoladex 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

CPP

- The choice of GnRH agonist formulation depends on patient and clinician preference. These preparations have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis (*Harrington and Palmert 2017)*.
  - In a multicenter trial with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse events (AEs) were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial *(Harrington and Palmert 2017, Rahhal et al 2009, Silverman et al 2015*).
  - A randomized controlled trial (RCT) with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups *(Fuld et al 2011).*
  - In a phase 3, randomized, open-label (OL) study (N = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses *(Lee et al 2012).*
  - Clinical trials with nafarelin demonstrated a reduction in the peak response of LH to GnRH stimulation from a pubertal response to a pre-pubertal response within 1 month of treatment. Additionally, breast development was arrested or regressed in 82% of girls, while genital development was arrested or regressed in 100% of boys *(Synarel Product Information 2017)*.
  - The efficacy of triptorelin 6-month injection was evaluated in an OL, single-arm clinical trial in females and males with CPP, ages 2 to 9 (N = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients *(Klein et al 2016)*.

Endometriosis

- A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis compared the safety and effectiveness of GnRH agonists to no treatment, placebo, danazol, intrauterine progestins, or other GnRH agonists (*Brown et al 2010*).
  - GnRH agonists were more effective than no treatment or placebo.
  - There was no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis.
  - There was a benefit in overall resolution for GnRH agonists compared with danazol.
  - There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel.
  - More AEs were reported in the GnRH agonist group.
  - No route of administration for GnRH agonists appeared to be superior to another.
- A RCT (N = 315) compared the efficacy of goserelin (3.6 mg every 28 days) to danazol 400 mg orally twice daily in females with endometriosis. Goserelin was found to be similar in efficacy and safety as compared to danazol. Both treatments significantly reduced mean subjective signs and symptoms scores during and after treatment *(Rock et al 1993).*
- A meta-analysis of 13 RCTs (N = 945) evaluated the effectiveness of GnRH agonists for endometriosis, with and without add-back therapy. Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid AEs that are caused by GnRH agonist-induced hormone suppression. The evidence suggested that add-back therapy was more effective for symptomatic relief than GnRH agonists alone, both immediately after

treatment and at 6 months. Add-back therapy increased estrogen levels, but did not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia *(Wu et al 2014)*.

- The FDA approval of elagolix was based on the results of the Elaris Endometriosis trials, EM-I and EM-II, which were 2 phase 3, 6-month, double-blind (DB), placebo-controlled (PC), RCTs in women 18 to 49 years of age with moderate to severe endometriosis. Three treatment groups, elagolix 150 mg orally daily (n = 475), elagolix 200 mg orally twice daily (n = 477), and placebo (n = 734) were evaluated for efficacy and safety. (*Orilissa Dossier 2018, Taylor et al 2017*).
  - Patients were considered responders if they experienced a reduction of ≥ -0.81 from baseline score in dysmenorrhea pain and a reduction of ≥ -0.36 from baseline score in NMPP, and no increase in rescue analgesic use. At months 3 and 6, a significantly greater proportion of women in both elagolix dose groups met the clinical response criteria for the co-primary endpoints of dysmenorrhea and NMPP ($p < 0.001$).
  - The most common AEs were hot flushes, headache, and nausea. Bone mineral density (BMD) loss was significantly greater than placebo in the 150 mg daily and 200 mg twice daily groups at 6 months. Liver and kidney function parameters/analytes exhibited sporadic statistically significant changes throughout treatment but none of the differences between the elagolix doses and placebo were considered clinically significant. Additionally, there was 1 suicide reported in the EM-II trial, which was related to overdose with multiple non-trial medications.
  - Patients who completed EM-I or EM-II continued on to 1 of the 2 phase 3 extension trials, EM-III or EM-IV. The duration of treatment was 6 months (with continuation of the same elagolix dose from the 6-month EM-I/EM-II trials, for a total of 12 months of treatment), followed by a 12 month observation period *(Surrey et al 2018)*.
    - The data from EM-III and EM-IV demonstrated that the response rates for dysmenorrhea and NMPP were maintained in women who continued treatment with elagolix. A decrease of 5 to 8% in lumbar spine BMD after 12 months of continuous treatment occurred in 2 to 3% of the 150 mg daily group and in 26 to 30% of the 200 mg twice daily group. The percentage of women with > 8% decrease in BMD in the lumbar spine, total hip, or femoral neck was 2 to 8% in the 150 mg daily group and 21% in the 200 mg twice daily group.

Uterine fibroids

- PEARL II was a DB, non-inferiority trial that included 307 patients randomly assigned to 5 or 10 mg of ulipristal vs leuprolide acetate depot, for 3 months of treatment. Uterine bleeding was controlled in 90% of patients receiving 5 mg of ulipristal acetate, in 98% of those receiving 10 mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2% (95% confidence interval [CI], -9.3 to 11.8) for 5 mg of ulipristal acetate and 8.8% (95% CI, 0.4 to 18.3) for 10 mg of ulipristal acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate, 5 days for those receiving 10 mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of ulipristal acetate, for 10% of those receiving 10 mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate ($p < 0.001$ for each dose of ulipristal acetate vs leuprolide acetate) *(Donnez et al 2012)*.

Infertility

- A meta-analysis of 73 RCTs (N = 12,212) compared the efficacy and safety of GnRH antagonists (cetrorelix or ganirelix) to long-course GnRH agonist regimens in patients using these agents for controlled ovarian hyperstimulation in ART (*Al Inany et al 2016*).
  - There was no evidence of a difference in live birth rate between GnRH antagonist and long-course GnRH agonist regimens in 2303 patients (odds ratio [OR] = 1.02; 95% CI, 0.85 to 1.23; 12 RCTs; $I^2 = 27\%$).
  - GnRH antagonists were associated with a lower incidence of any grade of ovarian hyperstimulation syndrome (OHSS) compared to GnRH agonists in 7944 patients (OR = 0.61; 95% CI, 0.51 to 0.72; 36 RCTs; $I^2 = 31\%$).
  - There was no difference in miscarriage rate per woman between the GnRH antagonist group and GnRH agonist group as evaluated in 7082 patients (OR = 1.03; 95% CI, 0.82 to 1.29; 34 RCTs; $I^2 = 0\%$).

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics (AAP): Evaluation and referral of children with signs of early puberty *(Kaplowitz and Bloch 2016)*
  - Treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant.
  - If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered.

- Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

Endometriosis

- ACOG: Updates Guideline on Diagnosis and Treatment of Endometriosis (*ACOG 2010, Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists can be used for the initial treatment of pain in women with suspected endometriosis.
    - However, recurrence rates are high after the medication is discontinued. Empiric therapy with another suppressive medication is an option. For example, empiric therapy with a 3-month course of a GnRH agonist is appropriate if the initial treatment with an oral contraceptive or NSAID is unsuccessful.
  - In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptives can be used to treat recurrent pain.
    - Oral or depot medroxyprogesterone acetate is also an effective treatment option.
    - If none of the above therapies is successful, then progestins, GnRH agonists, and androgens may be used.
    - The use of Mirena (levonorgestrel-releasing intrauterine system) reduces pelvic pain associated with endometriosis, but AEs are common.
  - If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain relief.
    - Add-back regimens have been used in women undergoing long-term therapy; they may include progestins alone, low dose progestins, progestins plus bisphosphonates, or estrogens.
- ASRM: Treatment of pelvic pain associated with endometriosis: A committee opinion *(ASRM 2014)*
  - Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.
  - Definitive diagnosis via laparoscopic surgery is recommended, with the option of treating visible endometriosis at that time.
  - Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
    - Surgical treatment with removal of the uterus and ovaries (total hysterectomy and bilateral salpingo-oophorectomy) is recommended in women with disabling symptoms who have completed childbearing and have failed to respond to multiple alternative regimens.

Uterine fibroids

- Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program: Management of Uterine Fibroids *(AHRQ 2017)*
  - GnRH agonists, mifepristone, ulipristal, and uterine artery embolism reduce fibroid size, and improve symptoms and quality of life. Myomectomy and hysterectomy also improve quality of life.
    - Moderate-strength evidence suggests that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms.
    - Low-strength evidence suggests that fibroid-related quality of life improves with GnRH agonists (with and without add-back therapy).
  - For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years was 6 to 7% after medical treatment or myomectomy and 44% after urinary artery embolization (UAE). For older women, the chance was 9 to 19% after medical treatment or UAE and 0% after myomectomy.
- ACOG: Alternatives to hysterectomy in the management of leiomyomas *(ACOG 2008)*
  - GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2 to 3 months preoperatively. Benefits of preoperative GnRH agonist administration should be weighed against their cost and side effects for individual patients.
  - Abdominal myomectomy is a safe and effective alternative to hysterectomy for the treatment of women with symptomatic leiomyomas.
  - Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

Infertility

- The 2018 ASRM guidelines for PCOS and a 2016 World Health Organization (WHO)-funded PCOS guidelines make the following recommendations *(Balen et al 2016, Teede et al 2018):*
  - Although off-label, letrozole is recommended as first-line therapy for ovulation induction in women with PCOS and anovulatory infertility.
  - Clomiphene is also considered a first-line treatment option in women with PCOS and anovulatory infertility. Per the ASRM guidelines, clomiphene could be used in preference to metformin, when treating an obese patient (BMI ≥ 30 kg/m^2). Both guidelines recommend the use of clomiphene in combination with metformin for PCOS patients with clomiphene resistance.
  - Gonadotropins can be used as second-line pharmacological agents in women with PCOS and anovulatory infertility who have failed oral ovulation induction therapy (clomiphene and/or metformin). No significant differences in efficacy between preparations of gonadotropin agents have been noted.
  - A GnRH antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle over a GnRH agonist long protocol. The preferred protocol is known to reduce the duration of stimulation, total gonadotropin dose, and incidence of OHSS.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Cetrotide carries the additional contraindication of severe renal impairment.
- Elagolix carries additional contraindications for known osteoporosis, severe hepatic impairment (Child-Pugh C), and concomitant use with strong OATP1B1 inhibitors (eg, cyclosporine and gemfibrozil).
- Lupaneta Pack carries additional contraindications, including undiagnosed uterine bleeding, breast-feeding, known/suspected/history of breast or other hormone-sensitive cancers, thrombotic/thromboembolic disorders, and liver tumors/liver disease.
- Lupron Depot carries additional contraindications, including undiagnosed abnormal uterine bleeding and breast-feeding.
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.

Warnings and Precautions

- An initial rise in gonadotropin and sex steroid levels may be seen during the first 2 to 4 weeks of therapy, due to the initial stimulatory effect of the drug (leuprolide, histrelin, triptorelin).
- Psychiatric events have been reported in patients taking GnRH agonists. Symptoms include crying, irritability, anger, and aggression (elagolix, histrelin, leuprolide, nafarelin, triptorelin). Suicidal ideation is an additional warning with elagolix.
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, or concomitant medications that may be associated with convulsions. Convulsions have also been reported in patients without the conditions mentioned above (leuprolide, histrelin, nafarelin, triptorelin).
- A reduction in BMD may be observed with most of the GnRH agonists/antagonists.
- Ovarian cysts have been reported during the first 2 months of therapy with Synarel and in post-marketing experience with Zoladex. Many, but not all, occurred in women with polycystic ovarian disease. These cystic enlargements may resolve after 4 to 6 weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Key Adverse Effects

- The common AEs within this medication class (excluding histrelin) include hot flushes/sweats, headache, depression/emotional lability, acne, decreased libido, insomnia, and weight gain.
- Injection site pain was one of the most commonly reported AEs for leuprolide. Implant site reaction, including discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion or swelling, was reported in 51% of patients in clinical trials with histrelin.
- Infections such as bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection were observed with triptorelin.

- In clinical trials, OHSS has been reported in 2.4% of patients treated with ganirelix and in 3.5% of patients treated with cetrorelix.

Drug Interactions

- Concomitant use of elagolix with a strong OATP1B1 inhibitor (eg. cyclosporine and gemfibrozil) is contraindicated.
- Concomitant use of elagolix with strong cytochrome P450 (CYP) 3A inhibitors should be limited to ≤ 1 month for the 200 mg twice daily dose and ≤ 6 months for the 150 mg daily dose. The co-administration of elagolix with inducers of CYP3A may decrease elagolix plasma concentrations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cetrotide (cetrorelix)	0.25 mg injection	SC	3 mg one time dose or 0.25 mg once daily	Dose should be adjusted based on individual response.
ganirelix	250 mcg injection	SC	Once daily	Dose should be adjusted based on individual response.
Lupaneta Pack (leuprolide/ norethindrone)	3.75 mg leuprolide syringe/5 mg norethindrone tablets 11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide 3.75 mg monthly or 11.25 mg once every 3 months for up to 6 months and norethindrone once daily for up to 6 months. Retreatment should be considered for up to another 6 months if endometriosis symptoms recur	Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on BMD.
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg once monthly or 11.25 mg once every 3 months, alone or in combination with norethindrone acetate Uterine leiomyomata: 3.75 mg once monthly or one 11.25 mg injection with concomitant iron therapy; 11.25 mg is indicated only for women for whom 3 months of hormonal suppression is deemed necessary	Duration of therapy for endometriosis is 6 months; duration of therapy for uterine leiomyomata is up to 3 months.
Lupron Depot-Ped (leuprolide acetate depot) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25, 30 mg (3-month)	Powder for injection	IM	CPP: Once monthly (7.5 mg, 11.25 mg, or 15 mg), or leuprolide 11.25 mg or 30 mg once every 3 months	The dose of Lupron Depot-Ped should be individualized for each patient. The dose should be increased to the next available dose if adequate hormonal and clinical suppression is not achieved

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with the fixed dosing starting dose.
Orilissa (elagolix)	Tablets	Oral	Once daily for the 150 mg dose (duration = 24 months); twice daily for the 200 mg dose in patients with co-existing dyspareunia (duration = 6 months)	A lower dose and duration of therapy is required for patients with moderate hepatic impairment (Child-Pugh Class B); elagolix is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Supprelin LA (histrelin)	Implant	SC	CPP: Once every 12 months	Implant injected in the inner aspect of the upper arm.
Synarel (nafarelin)	Nasal spray	Intranasal	CPP: Twice daily (up to 3 times daily when a dose increase is required) Endometriosis: Twice daily	Sneezing during or immediately after treatment should be avoided, as this may impair drug absorption. For the endometriosis indication, treatment should be started between days 2 and 4 of the menstrual cycle.
Triptodur (triptorelin)	Injection	IM	CPP: Once every 24 weeks	Response (LH levels or serum concentration of sex steroid levels) should be monitored beginning 1 to 2 months post therapy initiation and during therapy as necessary to confirm maintenance of efficacy.
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Once every 28 days for a total of 6 months Endometrial thinning: Once every 28 days for a total of 1 to 2 months	No adjustment necessary in renal or hepatic impairment. For the endometriosis indication, data are limited to patients ≥ 18 years of age treated for 6 months. Retreatment is not recommended.

Abbreviations: BMD = bone mineral density; CPP = central precocious puberty; IM = intramuscular; LH = luteinizing hormone; SC = subcutaneous

See the current prescribing information for full details

CONCLUSION

- CPP is characterized by the early onset of pubertal manifestations in girls and boys.
  - GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (LH and FSH) secretion and finally suppression of the release of gonadal sex hormones.
  - There are several FDA-approved GnRH agonists available in the form of implants, depot injections, and nasal spray. Depot formulations are generally preferred due to improved compliance. These GnRH agonists have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis.

- According to the AAP 2016 guidelines on the evaluation and referral of children with signs of early puberty, treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity.
  - A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis found no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis. However, a benefit in overall resolution for GnRH agonists compared with danazol was observed. Additionally, there was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel. No route of administration for GnRH appeared to be superior to another.
  - The safety and efficacy of Orilissa (elagolix), a recently approved oral GnRH antagonist, were demonstrated in 2 placebo-controlled studies in 1686 premenopausal women with moderate to severe endometriosis pain. In both studies, a higher proportion of women treated with elagolix were responders vs placebo for dysmenorrhea and NMPP in a dose-dependent manner at month 3 ($p \leq 0.001$ for all comparisons except non-menstrual pelvic pain with elagolix 150 mg once daily in study 2, $p \leq 0.01$).
  - ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists for the initial treatment of pain in women with suspected endometriosis. GnRH agonists can be used empirically in case of recurrence of endometriosis.
  - The 2014 ASRM guidelines recommend a definitive diagnosis via laparoscopic surgery, with the option of treating visible endometriosis at that time. Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.
  - AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low-strength evidence).
- Infertility is a common condition that can have a substantially negative emotional, physical, and financial impact on a couple. GnRH antagonists, such as cetrorelix and ganirelix, may be reserved for second-line treatment to prevent premature LH surges, allowing for controlled ovarian stimulation during ART procedures.
  - The 2018 ASRM guidelines for PCOS and 2016 WHO-funded PCOS guidelines recommend letrozole (off-label) or clomiphene for first-line therapy in women with PCOS who have anovulatory infertility. Gonadotropins are recommended as an option in anovulatory women with PCOS who have failed clomiphene (± metformin).

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Publication Date: February 13, 2019

Prior Authorization Guideline

Guideline Name Bone Density Regulators

1 . Indications

Drug Name: Evenity (romosozumab-aqqg injection)
Postmenopausal women with osteoporosis at high risk of fracture Indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
Drug Name: Prolia (denosumab)
Treatment of postmenopausal women with osteoporosis at high risk for fracture Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. **Treatment to increase bone mass in men with osteoporosis at high risk for fracture** Indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. **Treatment of bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer** Indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients

Prolia also reduced the incidence of vertebral fractures. NOTE: The use of Prolia for the treatment of bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer should not be confused with the use of Xgeva (another injectable formulation of denosumab) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors (including breast cancer and prostate cancer).

Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer Indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. NOTE: The use of Prolia for the treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer should not be confused with the use of Xgeva (another injectable formulation of denosumab) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors (including breast cancer and prostate cancer).

Treatment of Glucocorticoid-Induced Osteoporosis Indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Drug Name: Forteo (teriparatide injection), Teriparatide (teriparatide injection)

Postmenopausal women with osteoporosis at high risk of fracture Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, teriparatide reduces the risk of vertebral and nonvertebral fractures.

Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture Indicated to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Men and women with glucocorticoid-induced osteoporosis at high risk for fracture Indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Drug Name: Tymlos (abaloparatide injection)

Postmenopausal women with osteoporosis at high risk of fracture Indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Tymlos reduces the risk of vertebral fractures and nonvertebral fractures. Limitations of use: Because of the unknown relevance of the rodent osteosarcoma findings to

humans, cumulative use of Tymlos and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended.

2 . Criteria

Product Name: Evenity	
Approval Length	12 Months
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of postmenopausal osteoporosis or osteopenia

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 Bone mineral density (BMD) T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.1.2 One of the following:

2.1.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.1.2.2 Trial and failure, contraindication, or intolerance to one anti-resorptive treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab]) [B]

OR

2.2 Both of the following:

2.2.1 BMD T-score between -1.0 and -2.5 in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.2.2 One of the following:

2.2.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.2.2.2 Both of the following:

2.2.2.2.1 Trial and failure, contraindication, or intolerance to one anti-resorptive treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab])

AND

2.2.2.2.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

AND

3 - Trial of, contraindication, or intolerance to one of the following:

- Forteo (teriparatide)
- Tymlos (abaloparatide)

AND

4 - Treatment duration of Evenity (romosozumab-aqqg) has not exceeded a total of 12 months during the patient's lifetime

Notes	Evenity (romosozumab-aqqg) not to exceed the FDA-recommended treatment duration of 12 monthly doses.

Product Name: Prolia	
Diagnosis	Bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer
Approval Length	12 months
Therapy Stage	Initial Authorization

Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of nonmetastatic prostate cancer

AND

2 Patient is undergoing androgen deprivation therapy with one of the following:

2.1 Luteinizing hormone-releasing hormone (LHRH)/gonadotropin releasing hormone (GnRH) agonist [e.g., Eligard/Lupron (leuprolide), Trelstar (triptorelin), Vantas (histrelin), and Zoladex (goserelin)]

OR

2.2 Bilateral orchiectomy (i.e., surgical castration)

AND

3 One of the following:

3.1 Age greater than or equal to 70 years

OR

3.2 Both of the following:

3.2.1 Age less than 70 years

AND

3.2.2 One of the following:

3.2.2.1 Bone mineral density (BMD) scan T-score less than -1.0 (1.0 standard deviation or greater below the mean for young adults)

OR

3.2.2.2 History of one of the following resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

Product Name: Prolia	
Diagnosis	Bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer
Approval Length	12 months
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is undergoing androgen deprivation therapy with one of the following:

1.1 Luteinizing hormone-releasing hormone (LHRH)/gonadotropin releasing hormone (GnRH) agonist [e.g., Eligard/Lupron (leuprolide), Trelstar (triptorelin), Vantas (histrelin), and Zoladex (goserelin)]

OR

1.2 Bilateral orchiectomy (i.e., surgical castration)

AND

2 No evidence of metastases

AND

3 Patient is benefiting from therapy (e.g., improved or stabilized BMD, no new fractures, improved biochemical markers, etc.)

Product Name: Prolia	
Diagnosis	Bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer
Approval Length	12 months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of breast cancer

AND

2 Patient is receiving adjuvant aromatase inhibitor therapy (e.g., Arimidex [anastrozole], Aromasin [exemestane], Femara [letrozole])

AND

3 One of the following:

3.1 Bone mineral density (BMD) scan T-score less than -1.0 (1.0 standard deviation or greater below the mean for young adults)

OR

3.2 History of one of the following resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

AND

4 Trial and failure, intolerance, or contraindication to one bisphosphonate (e.g., alendronate)

Product Name: Prolia	
Diagnosis	Bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer
Approval Length	12 months [D]
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is receiving adjuvant aromatase inhibitor therapy (e.g., Arimidex [anastrozole], Aromasin [exemestane], Femara [letrozole])

AND

2 Patient is benefiting from therapy (e.g., improved or stabilized BMD, no new fractures, improved biochemical markers, etc.)

Product Name: Prolia	
Diagnosis	Postmenopausal women with osteoporosis or osteopenia at a high risk for fracture
Approval Length	24 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of postmenopausal osteoporosis or osteopenia

AND

2 One of the following:

2.1 Bone mineral density (BMD) scan indicative of osteoporosis: T-score less than or equal to -2.5 in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

OR

2.2 Both of the following:

2.2.1 BMD scan indicative of osteopenia: T-score between -1.0 and -2.5 (BMD T-score greater than -2.5 and less than or equal to -1.0) in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.2.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

OR

2.3 History of one of the following resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

AND

3 Trial and failure, intolerance, or contraindication to one bisphosphonate (e.g., alendronate)

Product Name: Prolia	
Diagnosis	Postmenopausal women with osteoporosis or osteopenia at a high risk for fracture
Approval Length	24 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is benefiting from therapy (e.g., improved or stabilized BMD, no new fractures, improved biochemical markers, etc.) without significant adverse effects

Product Name: Prolia	
Diagnosis	Increase bone mass in men at high risk for fracture
Approval Length	24 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is a male with osteoporosis or osteopenia

AND

2 One of the following:

2.1 Bone mineral density (BMD) scan indicative of osteoporosis: T-score less than or equal to -2.5 in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

OR

2.2 Both of the following:

2.2.1 BMD scan indicative of osteopenia: T-score between -1.0 and -2.5 (BMD T-score greater than -2.5 and less than or equal to -1.0) in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.2.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

OR

2.3 History of one of the following resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

AND

3 Trial and failure, intolerance, or contraindication to one bisphosphonate (e.g., alendronate)

Product Name: Prolia	
Diagnosis	Increase bone mass in men at high risk for fracture
Approval Length	24 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is benefiting from therapy (e.g., improved or stabilized BMD, no new fractures, improved biochemical markers, etc.) without significant adverse effects

Product Name: Prolia	
Diagnosis	Glucocorticoid-induced osteoporosis at high risk for fracture
Approval Length	24 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of glucocorticoid-induced osteoporosis

AND

2 Patient is initiating or continuing on greater than or equal to 7.5 mg/day of prednisone (or its equivalent) and is expected to remain on glucocorticoid therapy for at least 6 months

AND

3 One of the following:

3.1 BMD T-score less than or equal to -2.5 based on BMD measurements from lumbar spine, femoral neck, total hip, or radius (one-third radius site)

OR

3.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

OR

3.3 History of one of the following fractures resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

AND

4 Trial and failure, contraindication, or intolerance to one bisphosphonate (e.g., alendronate)

Product Name: Prolia	
Diagnosis	Glucocorticoid-induced osteoporosis at high risk for fracture
Approval Length	24 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Patient is benefiting from therapy (e.g., improved or stabilized BMD, no new fractures, improved biochemical markers, etc.) without significant adverse effects

Product Name: Forteo, Teriparatide	
Diagnosis	Postmenopausal osteoporosis or osteopenia, or men with primary or hypogonadal osteoporosis or osteopenia at high risk for fracture
Approval Length	24 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of one of the following:

- Postmenopausal osteoporosis or osteopenia
- Primary or hypogonadal osteoporosis or osteopenia

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 Bone mineral density (BMD) T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.1.2 One of the following:

2.1.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.1.2.2 Trial and failure, contraindication, or intolerance to one osteoporosis treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab])

OR

2.2 Both of the following:

2.2.1 BMD T-score between -1.0 and -2.5 in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.2.2 One of the following:

2.2.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.2.2.2 Both of the following:

2.2.2.2.1 Trial and failure, contraindication, or intolerance to one osteoporosis treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab])

AND

2.2.2.2.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

AND

3 - Treatment duration of parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) has not exceeded a total of 24 months during the patient's lifetime

Notes	Parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) not to exceed the FDA-recommended treatment duration of 2 years.

Product Name: Forteo, Teriparatide	
Diagnosis	Glucocorticoid-induced osteoporosis at high risk for fracture
Approval Length	24 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of glucocorticoid-induced osteoporosis

AND

2 - History of prednisone or its equivalent at a dose greater than or equal to 5 mg/day for greater than or equal to 3 months

AND

3 - One of the following:

3.1 BMD T-score less than or equal to -2.5 based on BMD measurements from lumbar spine, femoral neck, total hip, or radius (one-third radius site)

OR

3.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

OR

3.3 History of one of the following fractures resulting from minimal trauma:

- Vertebral compression fracture
- Fracture of the hip
- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus

AND

4 - Trial and failure, contraindication, or intolerance to one bisphosphonate (e.g., alendronate)

AND

5 - Treatment duration of parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) has not exceeded a total of 24 months during the patient's lifetime

Notes	Parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) not to exceed the FDA-recommended treatment duration of 2 years.

Product Name: Tymlos	
Diagnosis	Postmenopausal osteoporosis or osteopenia at high risk for fracture
Approval Length	24 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of postmenopausal osteoporosis or osteopenia

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 Bone mineral density (BMD) T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.1.2 One of the following:

2.1.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.1.2.2 Trial and failure, contraindication, or intolerance to one osteoporosis treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab])

OR

2.2 Both of the following:

2.2.1 BMD T-score between -1.0 and -2.5 in the lumbar spine, femoral neck, total hip, or radius (one-third radius site)

AND

2.2.2 One of the following:

2.2.2.1 History of low-trauma fracture of the hip, spine, proximal humerus, pelvis, or distal forearm

OR

2.2.2.2 Both of the following:

2.2.2.2.1 Trial and failure, contraindication, or intolerance to one osteoporosis treatment (e.g., alendronate, risedronate, zoledronic acid, Prolia [denosumab])

AND

2.2.2.2.2 One of the following FRAX (Fracture Risk Assessment Tool) 10-year probabilities:

- Major osteoporotic fracture at 20% or more in the U.S., or the country-specific threshold in other countries or regions
- Hip fracture at 3% or more in the U.S., or the country-specific threshold in other countries or regions

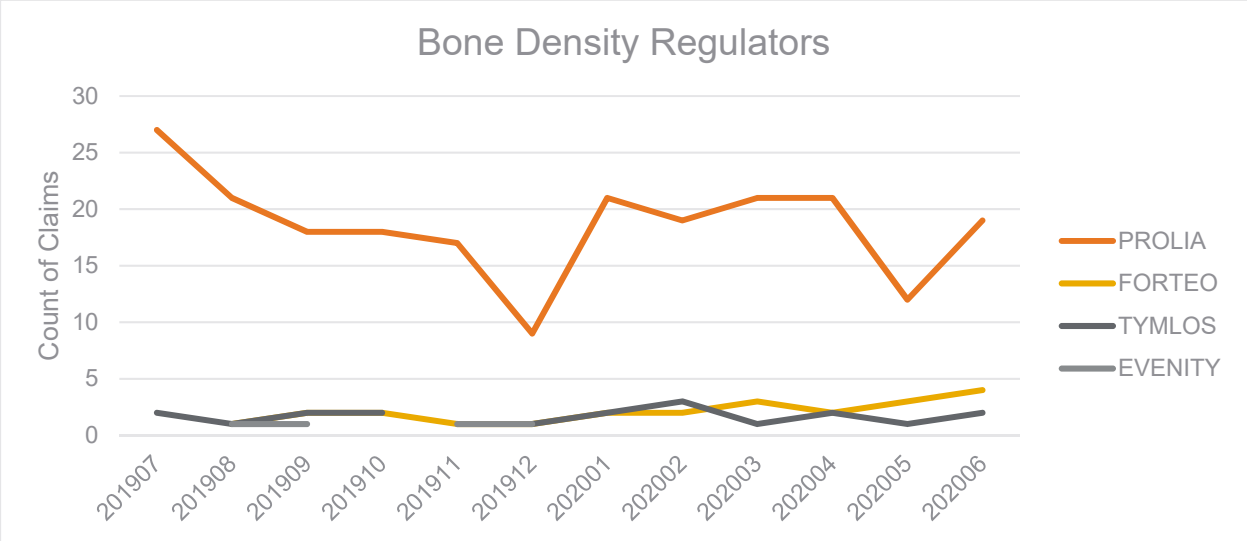
AND

3 - Treatment duration of parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) has not exceeded a total of 24 months during the patient's lifetime

Notes	Parathyroid hormones (e.g., teriparatide, Tymlos [abaloparatide]) not to exceed the FDA-recommended treatment duration of 2 years.

Nevada Medicaid
Bone Density Regulators
Fee for Service
July 1, 2019 – June 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
EVENITY	1	4	112	9.36
FORTEO	5	23	924	79.2
PROLIA	154	223	3,026	227
TYMLOS	4	19	570	29.64



OO. Prolia® (Denosumab)

Therapeutic Class: Bone Resorption Inhibitors (Osteoporosis Agents)
Last Reviewed by DUR Board: October 25, 2012

Prolia® (Denosumab) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board.

1. Coverage and Limitations

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

a. Postmenopausal Osteoporosis

1. The recipient has a T score $\leq$ -2.5; and

2. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture; and

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

b. Male Osteoporosis

1. The recipient has a T score $\leq$ -2.5; and

2. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture; and

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

c. Non-metastatic Prostate Cancer

1. The recipient has a history of osteoporotic fracture, or has multiple risk factors for fracture;

2. The recipient is receiving treatment with androgen-deprivation therapy (e.g., anti-androgen or luteinizing hormone-releasing hormone agents);

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

d. Breast Cancer

1. The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture;

2. The recipient is receiving adjuvant aromatase inhibitor therapy (e.g., anastrozole, exemestane and letrozole);

3. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

4. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate; or the recipient has had esophagitis; or the recipient is unable to remain upright.

2. 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.

PP. Forteo® (Teriparatide)

Therapeutic Class: Parathyroid/Bone Formation Stimulating Agent (Osteoporosis Agents)
Last Reviewed by DUR Board: October 25, 2012

Forteo® (Teriparatide) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board.

1. Coverage and Limitations

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

a. The recipient has been diagnosed with Postmenopausal Osteoporosis, or Glucocorticoid-Induced Osteoporosis, or the recipient is male and diagnosed with Primary or Hypogonadal Osteoporosis;

b. The recipient has a T score of $\leq$ 2.5;

c. The recipient has a history of osteoporotic fracture or has multiple risk factors for fracture;

d. The recipient has experienced an inadequate response, adverse event or has a contraindication to one bisphosphonate;

e. The recipient is not receiving any second line or third line osteoporosis therapy concurrently; and

f. The total duration of treatment with this agent has not exceeded two years.

2. 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.

INTRODUCTION

- Osteoporosis is the most common bone disease and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture (*Cosman et al 2014*). The National Osteoporosis Foundation (NOF) estimated that in 2010, 12 million people in the United States had osteoporosis, and more than 2 million osteoporosis-related fractures occur annually, with more than 70% of these occurring in women. Age is an important risk factor for bone loss; by age 60, half of white women have osteopenia or osteoporosis (*Camacho et al 2016*).
- According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person. Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score (*World Health Organization 1994, 2007*).
- Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis, and low bone mass is the primary indicator of fracture risk (*Camacho et al 2016*). Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death (*Cosman et al 2014*).
- To decrease the risk of fractures, the general population should be advised to consume 1200 mg of calcium and 800 to 1000 mg of vitamin D per day from dietary sources or supplements. All individuals should also participate in regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Strategies for preventing falls should be implemented when needed. Smoking cessation and avoidance of excessive alcohol intake are other initiatives to prevent osteoporosis (*Camacho et al 2016, Cosman et al 2014*).
- Bisphosphonates are used to prevent and treat postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis, and Paget's disease. There are several bisphosphonates approved for treatment of Paget's disease and malignancy-induced bone conditions, but not for osteoporosis. These agents include Aredia (pamidronate) zoledronic acid (Zometa) and Didronel (etidronate) (*Micromedex 2020*).
- Other agents used to treat osteoporosis include calcitonin (Miacalcin), an estrogen agonist/antagonist (Evista), the parathyroid hormone analogs (Forteo, Bonsity, and Tymlos), the receptor activator of nuclear factor K-B ligand inhibitor (Prolia), and the sclerostin inhibitor (Evenity). These agents also have other indications, such as: reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis; reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of Paget's disease; treatment of hypercalcemia; treatment of glucocorticoid-induced osteoporosis at high risk of fracture; treatment of bone loss in men receiving androgen deprivation therapy for prostate cancer; and treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Another parathyroid hormone analog is Natpara, which is an injectable form of recombinant parathyroid hormone. Natpara is FDA approved for the treatment of hypocalcemia in patients with hypoparathyroidism as an adjunct to calcium and vitamin D supplementation *(Micromedex 2020)*.
- Other agents in the estrogen agonist/antagonist class include Clomid or Serophene (clomiphene), tamoxifen, Fareston (toremifene), and Osphena (ospemifene). These agents have different indications, including: to induce ovulation in appropriately selected anovulatory women desiring pregnancy; the treatment and prevention of breast cancer; and treatment of women experiencing moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause (*Micromedex 2020*). These agents will not be discussed in this review.
- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab (Prolia), is also available as Xgeva This product is approved to prevent skeletal-related events in patients with bone metastases from solid tumors, treat hypercalcemia of malignancy refractory to bisphosphonates, and treat adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (*Micromedex 2020*). It will not be further discussed in this review. The Food and Drug Administration (FDA) has approved estrogen/hormone therapy for the prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. The Women's Health Initiative (WHI) found that 5 years of hormone therapy in the form of Prempro (conjugated estrogen/medroxyprogesterone) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% (*Writing Group for the WHI 2002*). However, the study also reported increased risks of myocardial infarction, stroke, invasive

breast cancer, pulmonary emboli, and deep vein thrombosis during 5 years of treatment. It is now recommended to use estrogen/hormone therapy in the lowest effective doses for the shortest duration necessary. Thus, these agents are not recommended for long-term prevention and will not be further discussed in this review.

- Medispan Class: Bone Density Regulators; Hormone Receptor Modulators

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bisphosphonates	
Actonel (risedronate)	✔
Atelvia (risedronate, delayed release tablet)	✔
Binosto (alendronate, effervescent tablet)	-
Boniva (ibandronate)	✔
Didronel (etidronate)*	✔
Fosamax (alendronate)	✔
Fosamax Plus D (alendronate/cholecalciferol)	-
Reclast (zoledronic acid)	✔
Calcitonin	
Miacalcin (calcitonin salmon) nasal solution*	✔
Estrogen Agonist-Antagonist	
Evista (raloxifene)	✔
Parathyroid Hormone Analogs	
Forteo, Bonsity (teriparatide)	-
Natpara (recombinant parathyroid hormone)**	-
Tymlos (abaloparatide)	-
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors	
Prolia (denosumab)	-
Sclerostin Inhibitor	
Evenity (romosozumab)	-

*Brand etidronate and calcitonin nasal spray are no longer marketed; products only available generically
**In September 2019, the manufacturer recalled this product due to concerns of the presence of rubber particulates. According to a January 21, 2020 update from the manufacturer, there is an expected delay of at least 1 year before the product becomes available in the US (*Takeda Pharmaceuticals 2020*).

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

INDICATIONS

Table 2. FDA Approved Indications for Bisphosphonates

Indication	alendronate* (Binosto, Fosamax, Fosamax Plus D)	etidronate (Didronel)	ibandronate* (Boniva)	risedronate* (Actonel, Atelvia)*	zoledronic acid* (Reclast)
Treatment of postmenopausal osteoporosis	✔		✔	✔	✔
Prevention of postmenopausal osteoporosis	✔ (Fosamax only)		✔ (tablets only)	✔ (Actonel only)	✔
Treatment to increase bone mass in men with osteoporosis	✔			✔ (Actonel only)	✔

Treatment of glucocorticoid-induced osteoporosis	✔ (Fosamax only)			✔ (Actonel only)	✔
Prevention of glucocorticoid-induced osteoporosis				✔ (Actonel only)	✔
Treatment of Paget's disease	✔ (Fosamax only)	✔		✔ (Actonel only)	✔
Treatment of heterotopic ossification due post hip replacement or spinal cord injury		✔			

* Limitations of use: The optimal duration of use has not been determined. The safety and effectiveness of Actonel, Reclast and Boniva (tablets) for the treatment of osteoporosis are based on clinical data of 3 years duration. The safety and effectiveness of Atelvia and Boniva injection for the treatment of osteoporosis are based on clinical data of 1 year duration. The safety and effectiveness of Binosto and Fosamax/Fosamax PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

(Prescribing information: Actonel 2019, alendronate solution 2019, Atelvia 2015, Binosto 2019, Boniva injection 2019, Boniva tablets 2016, etidronate 2017, Fosamax 2019, Fosamax Plus D 2019, Reclast 2017)

Table 3: FDA Approved Indications for Calcitonins, Estrogen Agonist-Antagonist, and Receptor Activator of Nuclear Factor K-B Ligand Inhibitor

Indication	Evista (raloxifene)	Evenity (romosozumab)	Miacalcin (calcitonin)	Prolia (denosumab)
Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause for whom alternative treatments are not suitable			✔	
Treatment of postmenopausal osteoporosis	✔			
Treatment of postmenopausal osteoporosis at high risk of fracture		✔		✔
Prevention of postmenopausal osteoporosis	✔			
Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis	✔			
Reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer	✔			
Treatment of Paget's disease			✔ (injection only)	
Treatment of hypercalcemia			✔ (injection only)	
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture				✔
Treatment to increase bone mass in men receiving androgen deprivation therapy for prostate cancer				✔
Treatment to increase bone mass in women receiving adjuvant aromatase inhibitor therapy for breast cancer				✔
Treatment to increase bone mass in men with osteoporosis at high risk for fracture				✔
Treatment of osteoporosis in patients who have failed or are intolerant to other therapies		✔		

(*Prescribing Information: Calcitonin salmon nasal spray 2019, Evenity 2019, Evista 2019, Miacalcin injection 2018, Prolia 2019*)

Table 4: FDA Approved Indications for Parathyroid Hormone Analogs

Indication	Forteo, Bonsity (teriparatide)	Natpara (recombinant parathyroid hormone)	Tymlos (abaloparatide)
Adjunct to calcium and vitamin D for hypocalcemia due to hypoparathyroidism		✔	
Treatment of postmenopausal osteoporosis at high risk of fracture	✔		✔
Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture	✔		
Treatment of glucocorticoid-induced osteoporosis at high risk of fracture	✔		

(*Prescribing Information: Bonsity 2019, Forteo 2019, Natpara 2018, Tymlos 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

Bisphosphonates

- Clinical trials for bisphosphonates included within this review evaluate their efficacy in increasing BMD and/or decreasing bone turnover markers (BTMs). Regardless of whether a patient is being treated for osteoporosis or has osteopenia and is receiving preventative treatment, the goal of therapy is to increase BMD and reduce the risk of fractures. Since both the treatment and prevention of osteoporosis focus on the same therapeutic outcomes, the data supporting the use of bisphosphonates for these indications has been summarized together.
- Head-to-head trials have resulted in conflicting data when comparing the efficacy among bisphosphonates.
  Data from trials and a meta-analysis specifically examining fractures indicate that bisphosphonates are efficacious and significantly lower the risk of developing fractures in both vertebral and nonvertebral areas, compared to placebo in both men and women (*Black et al 1996, Kanis et al 2005, Liu et al 2018, Lyles et al 2007, Ringe et al 2009, Sawka et al 2005*). Several meta-analyses have found that etidronate is effective for reducing the risk of vertebral fractures but not non-vertebral fractures when compared to placebo or calcium and vitamin D in postmenopausal women with osteoporosis (*Cranney et al 2001, Wells et al 2008).* Some evidence suggests that alendronate results in greater increases of BMD when compared to risedronate (*Bonnick et al 2006, Reid et al 2006, Reid et al 2008*). In an observational study, treatment with risedronate resulted in a greater reduction in the risk of nonvertebral and hip fractures compared to alendronate (*Silverman et al 2007*). In a small randomized trial (N = 50), once weekly alendronate demonstrated similar efficacy to daily risedronate (*Sarioglu et al 2006*). Zoledronic acid and alendronate 70 mg weekly had comparable increases in lumbar BMD over 1 year in a study with postmenopausal women with osteoporosis and over 2 years in a study of men with osteoporosis (*McClung et al 2007, Orwoll et al 2010*). Ibandronate was shown to reduce vertebral fractures more than alendronate and risedronate in 1 trial; however, 2 other trials demonstrated similar efficacy with ibandronate vs alendronate (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
  - Clinical trials have also established the efficacy of alendronate, risedronate, and zoledronic acid in patients with glucocorticoid-induced osteoporosis (*Mok et al 2008, Okada et al 2008, Reid et al 2009*). In a meta-analysis of 10 trials of alendronate in glucocorticoid-induced osteoporosis, the risk of fracture was not significantly affected despite significant improvements in BMD of the lumbar spine and femoral neck (*Wang et al 2018*). Few trials compare the efficacy of the bisphosphonates for the treatment of Paget's disease and glucocorticoid-induced osteoporosis. One such trial demonstrated that zoledronic acid is more effective than risedronate for the treatment of Paget's disease (*Reid et al 2005*).

- Based on the available evidence, and due to a lack of conclusive head-to-head data, it is unknown whether one agent is more efficacious than another and should be considered first-line for the treatment and prevention of osteoporosis.

- In terms of safety, a meta-analysis measuring bisphosphonate gastrointestinal (GI) adverse events (AEs) concluded that patients treated with zoledronic acid had a higher probability of any GI AE and nausea. However, etidronate had the highest probability of discontinuation due to GI AEs compared to the other oral formulations, risedronate was associated with a greater incidence of serious GI AEs, and alendronate was associated with a greater incidence of upper GI and esophageal AEs. Ibandronate was not included in the analysis (*Tadrous et al 2014*).
- Alendronate effervescent tablets (Binosto) have been shown to be bioequivalent to alendronate tablets (Fosamax). Therefore, clinical efficacy for this product is taken from clinical trials conducted for alendronate 10 mg per day and 70 mg per week (*Binosto prescribing information 2016*).
- In a Phase 3 non-inferiority trial comparing oral ibandronate 100 mg to intravenous ibandronate 1 mg, both therapies led to comparable gains in BMD after 12 months in all evaluable subgroups (*Hagino et al 2018*).
- A systematic review evaluated the efficacy and safety of bisphosphonates in Paget's disease. The analysis included 20 studies (N = 3168). A total of 10 studies specifically compared bisphosphonates (etidronate, tiludronate, ibandronate, pamidronate, olpadronate, alendronate, risedronate, zoledronate) to placebo, and found that bisphosphonates tripled the proportion (31% vs 9%) of patients whose bone pain disappeared (risk ratio [RR], 1.97; 95% CI, 1.29 to 3.01). Results were similar across all bisphosphonates evaluated (*Corral-Gudino et al 2017*).
- The effectiveness of etidronate for the treatment of heterotopic ossification due post hip replacement or spinal cord injury has been demonstrated through several studies (*Banovac et al 1993, Banovac et al 2000, , Stover et al 1976[a], Stover et al 1976[b], Thomas et al 1985*).

Calcitonin

- There is a lack of substantial clinical trial data for calcitonin; the body of evidence is primarily comprised of small observational trials (*Cadarette et al 2008, Chestnut et al 2000, Cranney et al 2002[b], Downs et al 2000, Hwang et al 2006, Kanis et al 1974, Woodhouse et al 1977*).
- Injectable calcitonin has demonstrated beneficial effects in the treatment of Paget's disease. Calcitonin therapy resulted in bone and symptom relief, increased mobility, and decreased alkaline phosphate and other BTMs. In addition, calcitonin has been shown to cause disease regression in some patients (*kaufa et al 1974, Woodhouse et al 1977*).
- Nasal calcitonin achieved significant increases in BMD at the lumbar spine compared to placebo after 6 months of therapy, which was maintained for up to 2 years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement (*Chestnut et al 2000, Downs et al 2000*). Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonin significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for nonvertebral fractures (*Hwang et al 2006*).

Estrogen Agonist-Antagonist

- Several placebo-controlled trials have demonstrated that treatment with raloxifene in postmenopausal women with osteoporosis significantly increases BMD. In addition, raloxifene demonstrated beneficial effects on lipid profile parameters (*Eastell et al 2009, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Siris et al 2005, Tanaka et al 2011*). In the MORE trial, raloxifene decreased the risk of vertebral fractures compared to placebo, with no observed difference in the rate of nonvertebral fractures (*Kung et al 2003*). There was also no difference in nonvertebral fracture rate during a 7 year follow-up of the MORE trial (*Siris et al 2005*). These data are supported by results of a meta-analysis of seven placebo-controlled trials, in which the reduction in the risk of vertebral fractures associated with raloxifene was inconsistent between 2 clinical trials, and neither trial demonstrated a reduction in the risk in nonvertebral fractures (*Eastell et al 2009*). When compared to bisphosphonate therapy, increases in BMD were significantly greater with alendronate compared to raloxifene (*Recker et al 2007*).
- In addition to evaluating the efficacy of raloxifene on bone, the MORE trial evaluated its efficacy in reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis. As a secondary end point, raloxifene reduced the incidence of newly diagnosed invasive breast cancer compared to placebo (*Cummings et al 1999*). In addition, the CORE trial evaluated the efficacy of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer, and over a total of 8 years, the incidence of invasive breast cancer and estrogen receptor-positive breast cancer was reduced by 66% and 76%, respectively, with raloxifene compared to placebo. In the placebo-controlled RUTH trial, raloxifene significantly reduced the risk of invasive breast cancer, as well as vertebral fractures, and did not significantly

affect the risk of coronary heart disease. Raloxifene, however, was associated with a higher risk of venous thromboembolism and fatal stroke (*Barrett-Connor et al 2006*).

- Raloxifene has also been compared head-to-head with the antineoplastic agent tamoxifen in reducing the risk of invasive breast cancer. In the STAR trial, raloxifene was shown to be as effective as tamoxifen in reducing the risk of invasive and noninvasive breast cancer, with a lower risk of thromboembolic events and cataracts after a median of 3.9 years. The risk of other cancers, fractures, ischemic heart disease, and stroke was similar between the 2 treatments (*Vogel et al 2006*). However, in a trial with a median follow-up of 6.75 years, tamoxifen was shown to significantly reduce the risk of invasive breast cancer compared to raloxifene. At this time, raloxifene significantly reduced the risk of invasive uterine cancer, uterine hyperplasia, and thromboembolic events. There was no difference in mortality rate between raloxifene and tamoxifen at the end of 3.9 years (*Vogel et al 2010*).
- In terms of safety data, raloxifene was most commonly associated with hot flashes and leg cramps. Several clinical trials reported thromboembolic events (*Bachmann et al 2011, Barrett-Conner et al 2006, Cadarette et al 2008, Cranney et al 2002[a], Cummings et al 1999, Eastell et al 2009, Ensrud et al 2006, Ettinger et al 1999, Johnston et al 2000, Kung et al 2003, Martino et al 2004, Recker et al 2007, Siris et al 2005, Tanaka et al 2011, Vogel et al 2006, Vogel et al 2010*).

Parathyroid Hormone Analogs

- A 2-year, placebo-controlled trial (N = 437) evaluating teriparatide in increasing bone mass in men with primary or hypogonadal osteoporosis was terminated early when a long-term toxicology trial noted an increase in the incidence of osteosarcoma in rats receiving teriparatide. After a median duration of 11 months, teriparatide significantly increased BMD at the lumbar spine and femoral neck compared to placebo (*Orwoll et al 2003*). In a follow-up of this trial, no serious safety concerns with teriparatide were observed (*Kaufman et al 2005*). Teriparatide has been compared to the bisphosphonate alendronate for the treatment of men with primary or hypogonadal osteoporosis. Specifically, when compared to alendronate and the combination of teriparatide plus alendronate, teriparatide significantly increased BMD at the posteroanterior spine, lateral spine, and femoral neck (*Finkelstein et al 2003*).
- Teriparatide also significantly increased BMD at the lumbar spine and total hip compared to alendronate in patients with glucocorticoid-induced osteoporosis. Additionally, significantly fewer patients receiving teriparatide had a vertebral fracture after 36 months (*Langdahl et al 2009, Saag et al 2007, Saag et al 2009*). Teriparatide was also compared to risedronate in men with glucocorticoid-induced osteoporosis. At 18 months, teriparatide was more effective at increasing BMD at the lumbar spine than risedronate (*Gluer et al 2013*).
- Teriparatide has been most extensively evaluated for the treatment of osteoporosis in postmenopausal women (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Hwang et al 2006, Kendler et al 2018, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Yuan et al 2019*). The double-blind, double-dummy, multicenter, randomized, controlled VERO trial enrolled 1360 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T score ≤ -1.50 (*Kendler et al 2018*). Patients were randomly assigned to receive 20 mcg of teriparatide once daily plus oral weekly placebo or 35 mg risedronate once weekly plus daily placebo injections for 24 months. The primary outcome was new radiographic vertebral fractures. Results revealed that new vertebral fractures occurred in 28 (5.4%) patients in the teriparatide group and 64 (12%) patients in the risedronate group (risk ratio, 0.44; 95% confidence interval [CI], 0.29 to 0.68; $p < 0.001$). Clinical fractures were also significantly reduced with teriparatide (4.8% vs 9.8%; $p = 0.0009$). The EUROFORS trial was a prospective, 2-year trial in which all patients received teriparatide for the first year of treatment. After 12 months, patients were divided into 2 substudies. In Substudy 1, for the second year of treatment, patients were randomized to teriparatide, the selective estrogen receptor modulator raloxifene, or no active treatment. In Substudy 2, all patients remained on teriparatide for the second year of treatment. After the first year of treatment, teriparatide significantly increased BMD at the lumbar spine, total hip, and femoral neck. The benefits of teriparatide appeared greater in antiresorptive treatment-naïve patients compared to treatment-experienced patients. Within Substudy 2, patients who continued teriparatide for a total of 2 years achieved significant increases in BMD after 24 months. Within Substudy 1, during the second year of treatment, BMD at the lumbar spine, total hip, and femoral neck continued to increase significantly with teriparatide. BMD at the lumbar spine did not change in patients who were switched to raloxifene; however, BMD at the total hip and femoral neck significantly increased. Patients who were switched to no active treatment had a significant decrease in BMD at the lumbar spine, no change in BMD at the total hip, and a significantly increased BMD at the femoral neck (*Eastell et al 2009, Minne et al 2008, Obermayer-Pietsch et al 2008*). In addition to significant increases in BMD, placebo-controlled trials demonstrate that teriparatide significantly reduces the risk of vertebral and nonvertebral fractures (*Body et al 2002, Lindsay et al 2004, Neer et al 2001*). Data also suggest that teriparatide in combination with a

bisphosphonate may result in significant increases in BMD compared to monotherapy with either teriparatide or a bisphosphonate (*Cosman et al 2009, Cosman et al 2011*). In another study of 12 months duration, combined teriparatide plus denosumab were compared to either treatment alone. Combination therapy was associated with significantly greater BMD increases at the posterior-anterior spine, femoral neck, and hip than either drug alone (*Leder et al 2014, Tsai et al 2013*).

- A systematic review and meta-analysis of 23 RCTs examining upper limb and hip fractures found a significant reduction in hip fractures with teriparatide compared to either placebo or other medications (odds ratio [OR], 0.44; 95% CI, 0.22 to 0.87; p=0.019); however, no difference was seen in reduction of humerus, forearm, or wrist fractures *(Diez-Perez et al 2019)*. A second systematic review of 17 studies showed that teriparatide reduced vertebral and nonvertebral fractures when compared to placebo but did not reduce wrist and hip fractures *(Chen et al 2019)*. Additionally, there was no difference in fracture risk reduction between teriparatide and other medications.
- In terms of safety data, no clinically significant concerns related to teriparatide were observed; however, treatment was associated with a higher rate of hypercalcemia compared to placebo and bisphosphonate therapy. No cases of osteosarcoma were reported (*Body et al 2002, Cosman et al 2009, Cosman et al 2011, Eastell et al 2009, Finkelstein et al 2003, Finkelstein et al 2006, Hwang et al 2006, Kaufman et al 2005, Langdahl et al 2009, Lindsay et al 2004, McClung et al 2005, Minne et al 2008, Neer et al 2001, Obermayer-Pietsch et al 2008, Orwoll et al 2003, Saag et al 2007, Saag et al 2009*).
- The efficacy of abaloparatide was compared with teriparatide and placebo in the 18-month randomized controlled ACTIVE trial in 2463 postmenopausal women with osteoporosis. Treatment with abaloparatide resulted in a significant reduction in new morphometric vertebral and nonvertebral fractures vs placebo, while treatment with teriparatide also resulted in a significant reduction in new morphometric vertebral fractures vs placebo. For reduction in nonvertebral fractures, treatment with abaloparatide was not statistically different from teriparatide. The incidence of hypercalcemia was significantly lower with abaloparatide vs teriparatide (*Miller et al 2016*). The ACTIVExtend open-label extension trial evaluated 6 months of follow-up therapy with alendronate 70 mg once weekly in both the abaloparatide and placebo groups, and demonstrated that the treatment cycle with abaloparatide for 18 months followed by alendronate reduced new morphometric vertebral fractures by 87%, nonvertebral fractures by 52%, clinical fractures by 45%, and major osteoporotic fractures by 58% vs placebo and alendronate (*Cosman et al 2017*).
- Several RCTs have examined the effect of recombinant parathyroid hormone on BMD. In 2 RCTs, recombinant parathyroid hormone significantly increased BMD at 12 and 18 months in postmenopausal women with osteoporosis compared to placebo; however, 1 of these RCTs found a decrease in BMD at the forearm at 18 months *(Greenspan et al 2007, Hodsman et al 2003).* There are several studies examining the effect of recombinant parathyroid hormone on BMD in patients with hypoparathyroidism, but these studies generally include small sample sizes or lack a comparator arm. Results have been inconsistent in showing an increase in BMD, and 2 of these studies have shown a decrease in BMD at the hip, spine, whole body, or radius *(Cusano et al 2013, Rubin et al 2016, Sikjaer et al 2011).*

Receptor Activator of Nuclear Factor K-B Ligand Inhibitors

- The safety and efficacy of denosumab for the treatment of bone loss in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer were established in a 2 year, double-blind, placebo-controlled, randomized trial enrolling 252 women (*Ellis et al 2008*). Patients were randomized to subcutaneous denosumab every 6 months (n = 127) or placebo (n = 125) for a total of 4 doses; all patients received supplemental calcium and vitamin D. Overall, denosumab increased BMD at the lumbar spine at 12 and 24 months by 5.5% and 7.6%, respectively, compared to placebo ($p < 0.0001$ at both time points). BMD at the lumbar spine was significantly higher with denosumab compared to placebo after 12 months (4.8% vs -0.7%; treatment difference, 5.5%; 95% CI, 4.8 to 6.3; $p < 0.0001$). Furthermore, after 2 years, denosumab increased BMD at the lumbar spine (-1.4% placebo, +4.8% denosumab), total hip (-1.0% placebo, +3.8% denosumab), and femoral neck (-0.8% placebo, +2.8% denosumab).
- A double-blind, placebo-controlled, Phase 3 trial evaluated denosumab vs placebo in 3420 postmenopausal women with early hormone-receptor positive breast cancer receiving treatment with aromatase inhibitors (*Gnant et al 2015*). Women were randomized to denosumab 60 mg every 6 months or placebo. The primary outcome measure of time to first fracture was significantly delayed in the denosumab group compared to placebo (hazard ratio [HR], 0.50; 95% CI, 0.39 to 0.65; $p < 0.0001$). The incidence of AEs was similar in both treatment groups.
- When compared to placebo, denosumab significantly prolonged bone-metastasis-free survival (composite of time to first occurrence of bone metastasis and death from any cause) in men with non-metastatic prostate cancer (treatment difference, 4.2 months; HR, 0.85; 95% CI, 0.73 to 0.98; $p = 0.028$). There was no difference in overall survival observed

between the 2 treatment groups. In this trial, BMD evaluations were not performed; however, it was noted that biochemical markers of bone turnover significantly decreased with denosumab compared to placebo ($p < 0.001$ for all). Of note, the FDA-approved dosing was not evaluated in this trial; denosumab was administered once monthly (*Smith et al 2012*). The ADAMO trial showed that denosumab therapy administered every 6 months continued to increase BMD in men with low BMD throughout the second year of treatment (*Langdahl et al 2015*).

- Of the available clinical trial data evaluating the safety and efficacy of denosumab in postmenopausal women with osteoporosis who are at high risk of fracture, only one placebo-controlled trial (the FREEDOM trial) demonstrated a reduction in the risk of fracture with denosumab. In this trial, after 36 months, there were significant reductions with denosumab compared to placebo in the incidence of new vertebral (2.3% vs 7.2%; relative risk [RR], 0.32; 95% CI, 0.26 to 0.41; $p < 0.001$), nonvertebral (6.5% vs 8%; RR, 0.80; 95% CI, 0.67 to 0.95; $p = 0.01$), and hip fractures (0.7% vs 1.29%; RR, 0.6; 95% CI, 0.31 to 0.97; $p = 0.04$) (*Cummings et al 2009*). A 3-year extension trial maintained patients randomized to denosumab on active treatment for a total of 6 years and crossed over the placebo patients to denosumab treatment for a total of 3 years. For patients on denosumab for 6 years, BTMs were maintained at lower than pretreatment levels and BMD continued to increase. Fracture incidence in the long-term group remained low and below the rates reported in the FREEDOM placebo group. For the cross-over group, data obtained were consistent with FREEDOM observations (ie, rapid and marked reduction in BTMs, large increases in BMD, low fracture rates, favorable benefit/risk profile) (*Bone et al 2013*). A 7-year extension of FREEDOM, for a total of 7 to 10 years of exposure to denosumab, further confirmed a low fracture incidence rate with low rates of AEs (*Bone et al 2017*). Additionally, BMD at the lumbar spine, total hip, femoral neck, and radius continued to increase, suggesting no plateau to BMD benefits with denosumab.
- A meta-analysis/systematic review of clinical trials of denosumab in osteopenic and osteoporotic postmenopausal women with low bone mass sought to evaluate the effect of denosumab on BTMs and BMD. In this analysis, AEs, including fracture risk, were also evaluated as secondary endpoints. Due to missing or unavailable data, it was not possible for the investigators to evaluate the efficacy of denosumab based on change in baseline BMD. Treatment with denosumab was associated with increased BMD at the lumbar spine and hip, as well as decreased BTMs. Regarding secondary outcomes, denosumab did not demonstrate a significant reduction in fracture risk (OR, 0.74; 95% CI, 0.33 to 0.64; $p = 0.45$) (*Anastaskilakis et al 2009*).
- The efficacy of denosumab for increasing BMD is also supported by 3 dose-ranging, placebo-controlled trials, as well as a head-to-head trial with the bisphosphonate, alendronate (*Brown et al 2009, Lewiecki et al 2007, McClung et al 2006, Miller et al 2008[b]*). The 3 dose-ranging trials demonstrated that 48 months of denosumab therapy significantly increased BMD at all measured skeletal sites (lumbar spine, total hip, and distal 1/3 radius) ($p < 0.001$), and achieved potent and sustained reductions of BTMs compared to placebo (*Cummings et al 2009*). In a small subset of patients who discontinued treatment with denosumab, subsequent decreases in BMD at measured skeletal sites were observed. When compared to alendronate, changes in BMD at the total hip were also significantly greater with denosumab at 12 months (3.5% vs 2.6%; $p < 0.0001$) (*Brown et al 2009*). In a second meta-analysis comparing denosumab to weekly alendronate, no difference in fracture risk was demonstrated (OR, 1.42; 95% CI, 0.84 to 2.40; $p = 0.19$); however, both treatments were associated with significantly increased BMD at distal radius, total hip, lumbar spine, and femoral neck after 6 months (*Lin et al 2012*). In a 12-month trial comparing denosumab to monthly ibandronate therapy, treatment with denosumab resulted in significantly greater BMD increases at the total hip, femoral neck, and lumbar spine compared with ibandronate (*Recknor et al 2013*).
- A systematic review and meta-analysis assessed the efficacy and safety of denosumab compared to other anti-osteoporosis agents (eg, bisphosphonates, teriparatide) in patients previously treated with other medications (*Fontalis et al 2018*). Results demonstrated the superiority of denosumab in augmenting BMD at all skeletal sites studied (treatment difference in total hip [primary outcome], 1.59%; 95% CI, 1.01 to 2.17) compared to controls, whereas the overall incidence of serious AEs was not increased ($p = 0.42$). Similar results were demonstrated in another meta-analysis comparing denosumab to bisphosphonates for the treatment of postmenopausal osteoporosis. In this analysis, denosumab significantly increased the change in total hip, femoral neck, and lumbar spine BMD when compared to bisphosphonates. Denosumab did not yield any increased benefit for reducing fracture risk when compared to bisphosphonates and both denosumab and bisphosphate therapy demonstrated a similar incidence of AEs and withdrawals due to AEs (*Wu et al 2018*).
- The impact of denosumab compared to risedronate on BMD was evaluated in 795 patients with glucocorticoid-induced osteoporosis. At 24 months, the increase in lumbar spine and total hip BMD was significantly higher with denosumab compared to risedronate in patients on glucocorticoids for less than 3 months (mean percentage change: 4.5% for the

lumbar spine, 3.1% for the total hip, and 2.5% for the femoral neck) as well as for those taking glucocorticoids for greater than 3 months (mean percentage change: 3.2% for the lumbar spine, 2.5% for the total hip, and 1.8% for the femoral neck). The incidence of discontinuation of treatment due to AEs was 7.9% with denosumab and 9.6% with risedronate. Fractures were reported in 8.8% in the denosumab group (4.4% vertebral, 5.3% non-vertebral) and 9.1% of patients taking risedronate (6.9% vertebral, 3.8% non-vertebral). The incidence of infection was approximately 36% in both groups (*Saag et al 2019*).

- A systematic review and meta-analysis assessed the effect of denosumab vs bisphosphonate treatment on BMD, fractures and safety in patients with glucocorticoid-induced osteoporosis . Collective data from 3 clinical trials demonstrated that one year of denosumab therapy increased lumbar (2.32%, 95% CI, 1.73% to 2.91%, p<0.0001) and hip (1.52%, 95% CI, 1.1% to 1.94%, p<0.0001) BMD more than bisphosphonates . The analysis found similar rates of fracture incidence, AEs and, infection between both treatments (*Yanbeiy and Hansen 2019).*
- In terms of safety data, no clinically significant concerns related to denosumab were observed; the safety profile of denosumab appears similar to that of bisphosphonates (*Anastaskilakis et al 2009, Brown et al 2009, Cummings et al 2009, Lewiecki et al 2007, Lin et al 2012, McClung et al 2006, Miller et al 2008[b], Smith et al 2012*).

Sclerostin Inhibitors

- The efficacy of romosozumab in postmenopausal women with osteoporosis was demonstrated in 2 clinical trials. When compared with placebo, romosozumab significantly decreased vertebral and clinical fractures; however, there was no statistically significant difference in nonvertebral fractures between patients receiving placebo or romosozumab *(Cosman et al 2016)*. In a trial comparing 24 months of alendronate with 12 months of romosozumab followed by 12 months of alendronate, a significant reduction in new vertebral fracture risk was observed in the romosozumab treatment group at 24 months. Additionally, patients receiving romosozumab followed by alendronate had a lower risk of new vertebral fracture, clinical fracture, hip fracture, and nonvertebral fracture, which was significant compared to the alendronate only group *(Saag et al 2017)*.
- An RCT examining the use of romosozumab in men > 50 years of age with osteoporosis and a history of fragility fracture showed a significant increase in BMD at the spine and hip compared to placebo *(Lewiecki et al 2018).*

Comparative Efficacy

- From the Agency for Healthcare Research and Quality (AHRQ) evaluation (*Crandall et al 2012*), the following conclusions were reached:
  - Calcitonin was excluded because the reviewers found that it should no longer be considered appropriate therapy for osteoporosis.
  - There is a high level of evidence from randomized controlled trials (RCTs) that alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, and raloxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis.
  - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid and denosumab reduce the risk of nonvertebral fractures in postmenopausal women with osteoporosis; there is moderate evidence that teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
  - There is a high level of evidence from RCTs that alendronate, risedronate, zoledronic acid, and denosumab reduce the risk of hip fractures in postmenopausal women with osteoporosis.
  - There is insufficient evidence from head-to-head trials with bisphosphonates to support the superiority of one agent over the others for the prevention of fractures.
  - The evidence is insufficient regarding the use of combination therapy or sequential use of osteoporosis therapies in relation to fracture outcomes.
  - Evidence is insufficient regarding the effectiveness of therapies to prevent or treat osteoporosis in men.
  - Evidence is insufficient regarding the effect of glucocorticoid treatment on response to therapies.
  - About half of patients appeared to show persistence with osteoporosis treatment at 1 year.
  - Adverse effects of concern identified from the report included the following:
    - A relationship between zoledronic acid and atrial fibrillation is unproven but still an area of active surveillance.
    - Evidence is high for an increased risk for venous thromboembolic events (eg, pulmonary embolism) and vasomotor symptoms (eg, hot flashes) with raloxifene therapy.
    - Evidence is insufficient regarding the risk of esophageal cancer with bisphosphonates.

    - Evidence is high regarding the risk for alendronate and mild upper GI events (acid reflux, esophageal irritation, nausea, vomiting, and heartburn).
    - Evidence is high that the prevention and treatment of osteoporosis with bisphosphonates remains a relatively minor contributor to the development of osteonecrosis of the jaw.
    - The risk remains low for atypical, low-trauma subtrochanteric fragility fractures of the femur with long-term use of bisphosphonates for prevention or treatment of osteoporosis compared with the numbers of osteoporotic fractures prevented by bisphosphonate therapy.
    - Evidence is high for rashes, injection site reactions, and infection with denosumab.
    - A 2016 surveillance report of the document summarized new evidence with respect to AEs that were not reported in the original report. (*Agency for Healthcare Research and Qualilty 2016*). These include risk of:
        - Cerebrovascular accident, myocardial infarction, GI events, death, arrhythmia, dyspnea, and hypertension with teriparatide.
        - Headache, dizziness, arthritis/arthralgia, and hypotension with raloxifene.
        - Dermatological conditions and falls with denosumab.
- There is a lack of substantial head-to-head data comparing calcitonin to other established osteoporosis treatments. In 2 clinical trials, bisphosphonate and parathyroid hormone analog therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon (*Downs et al 2000, Hwang et al 2006*).
- A network meta-analysis found that zoledronic acid significantly increased BMD in lumbar spine and teriparatide decreased fracture rates in men with osteoporosis when compared to other agents such as alendronate, ibandronate, and risedronate (*Chen et al 2015*).
- A network meta-analysis performed indirect comparisons to determine the likelihood of each drug being the most preferable for various outcomes (*Yang et al 2016*). Among products included in this study, the most preferred agents for various outcomes were teriparatide in nonvertebral fractures; denosumab, zoledronic acid, and alendronate in hip fractures; teriparatide in wrist fractures; and raloxifene, alendronate, and denosumab for AEs.
- A systematic review and meta-analysis demonstrated teriparatide to be superior to alendronate in increasing lumbar spine BMD in patients with postmenopausal osteoporosis. The results of the meta-analysis showed no significant difference in the change from baseline in femoral neck BMD or incidence of vertebral and/or nonvertebral fractures between the 2 therapies (*Wang et al 2017[a]*).
- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) evidence report included a network meta-analysis of 3 RCTs to evaluate the comparative safety and efficacy of teriparatide, abaloparatide, and zoledronic acid for treatment of osteoporosis in postmenopausal women at high risk for fracture The analysis determined that teriparatide and abaloparatide were not significantly different from each other or zoledronic acid in reducing morphometric vertebral or nonvertebral fractures, and safety issues had little influence on the net benefit for each therapy compared to each other (*CTAF 2017*).
- A systematic review and meta-analysis demonstrated significantly lower risk of vertebral fractures with alendronate and risedronate in men with osteoporosis, but not with injectable calcitonin or denosumab vs controls. For bisphosphonates as a treatment category, meta-analyses demonstrated a significantly lower risk of vertebral fractures and possible nonvertebral fractures vs controls (*Nayak et al 2017*).
- A network meta-analysis identified parathyroid hormone therapy (teriparatide) and zoledronic acid as agents with the highest probability of satisfactory performance in preventing vertebral fractures in postmenopausal women in the final relative ranking of interventions among 10 osteoporosis agents, including oral bisphosphonates, denosumab, raloxifene, and strontium ranelate. For prevention of clinical vertebral fractures, zoledronic acid was determined to be the most effective, with denosumab as a second option, when compared to placebo. There were no significant differences between therapies identified with respect to adverse effects (*Wang et al 2017[b]*).
- A prospective cohort study of 32 patients with glucocorticoid-induced osteoporosis found that denosumab 60 mg subcutaneously every 6 months was superior to alendronate 35 mg orally once weekly in increasing lumbar spine BMD at 12 months ($p < 0.05$) (*Iseri et al 2018*).
- A systematic review of 6 RCTs found significant improvement in bone strength in postmenopausal women with osteoporosis receiving denosumab compared to bisphosphonates at 12 months in 4 of the 6 studies; however, bone turnover marker was consistently lower in patients receiving denosumab (*Chandran et al 2019)*
- A systematic review and meta-analysis of 16 trials (N=18,940) evaluated the impact of bone anabolic therapies (teriparatide, abaloparatide, romosozumab) compared to bisphosphonates or placebo on fractures (primary outcome), BMD, and bone markers in patients with postmenopausal osteoporosis. Abaloparatide ranked better than other active

treatments for reduction in vertebral and non-vertebral fractures. For the secondary outcome of increase in BMD, romosozumab ranked highest for all BMD locations compared to other active treatments. Compared to other treatments, teriparatide had the greatest impact on bone formation markers. However, about 30% of the trials in this analysis were found to have a high risk of bias (*Hernandez 2019*).

CLINICAL GUIDELINES

- To prevent and/or treat osteoporosis in postmenopausal women and men, national guidelines recommend adequate calcium and vitamin D intake, weight bearing exercise, cessation of smoking, and limiting alcohol intake (*ACOG 2012 [reaffirmed in 2019], Adler et al 2016, Buckley et al 2017, Camacho et al 2016, Conley 2020, Cosman et al 2014, Eastell et al 2019, Qaseem et al 2017, Watts et al 2012*).
- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Eastell et al 2019, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*).
  - Bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) are generally considered first-line therapy. Clinical trials have not consistently shown one agent to be more effective than another. Because etidronate is not approved for the indication of prevention or treatment of osteoporosis, many guidelines do not recommend its use *(ACOG 2012, Adler et al 2016, Camacho et al 2016, Cosman et al 2014, Qaseem et al 2017, Watts et al 2012)*.
  - While some national guidelines recommend denosumab as an alternative to bisphosphonates (*ACOG 2012, Eastell et al 2019*), the American Association of Clinical Endocrinologists (AACE) recommends denosumab as an optional first-line treatment in postmenopausal women (*Camacho et al 2016*).
  - Teriparatide is generally reserved for patients at high risk for fractures, or unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). The Endocrine society has recommended abaloparatide or teriparatide as treatment options in postmenopausal women at very high risk of fracture (*Eastell et al 2019).*
  - Although calcitonin and raloxifene are approved for osteoporosis, they are not considered first-line therapies due to AEs, less evidence of efficacy, and/or route of administration.
  - A recent guideline from the American Society for Bone and Mineral Research (ASBMR) specifically geared toward secondary fracture prevention in patients 65 years of age and older recommends the following for pharmacologic therapy (*Conley et al 2020*):
    - Oral alendronate or risedronate as first-line treatment (considered well-tolerated and available at a low cost). Intravenous zoledronic acid or subcutaneous denosumab are recommended if oral bisphosphonates cannot be used.
    - Patients at high-risk (specifically after vertebral fractures): consider anabolic therapies in consultation with a specialist.
    - Optimal duration of treatment is unknown but general recommendation is 3 to 5 years due to potential risk of rare adverse events that increase with longer duration of treatment.
    - Consider risks and monitor for atypical femoral fractures and osteonecrosis of the jaw.
- Patients with chronic kidney disease (CKD) grades 3a to 3b with parathyroid hormone in the normal range and osteoporosis and/or high risk of fracture should receive treatment similar to that of the general population (*Ketteler et al 2018*).
- According to the Endocrine Society guideline for Paget's disease, treatment with bisphosphonates is recommended for most patients with active or symptomatic Paget's disease who are at risk of future complications. A single 5 mg dose of intravenous zoledronic acid is recommended as the preferred initial agent in patients with no contraindications (*Singer et al 2014*).

SAFETY SUMMARY

- **Contraindications**
  - Bisphosphonates
    - Oral agents: Abnormalities of the esophagus that delay esophageal emptying (eg, stricture or achalasia)
    - Oral agents: Inability to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate)
    - Hypocalcemia
    - Clinically overt osteomalacia (etidronate)

        - Creatinine clearance <35 mL/min or acute renal impairment (zoledronic acid)
    - Alendronate oral solution
        - Patients at increased risk of aspiration
    - Raloxifene
        - Active or past history of venous thromboembolism
        - Pregnancy or nursing mothers
    - Denosumab
        - Hypocalcemia
        - Pregnancy or nursing mothers
    - Romosozumab
        - Hypocalcemia

- **Warnings/precautions**
    - Bisphosphonates
        - Caution should be used in patients with active GI problems (except zoledronic acid)
        - Reports of severe and occasionally incapacitating bone, joint, and/or muscle pain
        - Osteonecrosis of the jaw
        - Caution should be used in aspirin-sensitive patients (zoledronic acid)
        - Caution should be used in patients who must restrict sodium intake (alendronate effervescent tablets)
        - Hypocalcemia must be corrected prior to use
        - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
        - Patients receiving Atelvia should not be treated with Actonel, as both products contain the same active ingredient
        - Renal toxicity may occur in patients with pre-existing renal impairment receiving ibandronate injection
    - Raloxifene
        - **Boxed warning:** Increased risk of venous thromboembolism and death from stroke
        - Venous thromboembolism: increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue 72 hours prior to and during prolonged immobilization
        - Death due to stroke
        - Should not be used for the primary or secondary prevention of cardiovascular disease
        - Not recommended in premenopausal women
        - Caution should be used in patients with hepatic impairment
        - Concomitant use with systemic estrogens is not recommended
        - Hypertriglyceridemia; serum triglycerides should be monitored throughout treatment for women with a history of marked hypertriglyceridemia receiving treatment with raloxifene and oral estrogen or estrogen plus progestin
    - Parathyroid Hormone Analogs
        - **Boxed warning:** Parathyroid hormone analogs should not be used in patients at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, prior external beam or implant radiation involving the skeleton, and in pediatric and young adult patients with open epiphyses)
            - Cumulative lifetime use of abaloparatide and/or teriparatide > 2 years not recommended
            - Recombinant parathyroid hormone should only be used in patients that are unable to be controlled on calcium and vitamin D
        - Orthostatic hypotension
        - Caution should be used in patients with active or recent urolithiasis
        - Hypercalcemia
        - Hypocalcemia following discontinuation of recombinant parathyroid hormone
    - Calcitonin
        - Potential increased risk of malignancies
        - Circulating antibodies and abnormal urine sediment
        - Hypocalcemia
        - Nasal spray: Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status recommended at beginning of treatment, periodically during the course of therapy, and at any time nasal symptoms occur
    - Denosumab

        - Atypical, low-energy, or low trauma fractures of the femoral shaft
        - Osteonecrosis of the jaw
        - Severe musculoskeletal pain
        - An increased risk for multiple vertebral fractures has been reported following discontinuation of denosumab
        - Increased risk for serious infections in patients on concomitant immunosuppressant agents or with impaired immune systems
        - Patients receiving Prolia should not be treated with Xgeva, as both products contain the same active ingredient
        - Hypersensitivity reactions, including anaphylaxis, may occur
        - Hypocalcemia must be corrected prior to use. Concomitant use of calcium-lowering drugs or calcimimetic drugs may increase risk of hypocalcemia.
        - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
        - Dermatologic reactions, including dermatitis, rash, and eczema have been reported, and may require discontinuation of the drug
        - Significant suppression of bone remodeling may occur and may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing
    - Romosozumab
        - **Boxed warning:** There may be an increase in risk of myocardial infarction, stroke, and cardiovascular death. Romosozumab should not be used in patients with a stroke or myocardial infarction within the past year and should be discontinued if events occur during therapy.
        - Major adverse cardiac events may occur
        - Hypersensitivity reactions may occur
        - Hypocalcemia must be corrected prior to use
        - Osteonecrosis of the jaw
        - Atypical femur fractures have been reported; patients with new thigh or groin pain should be evaluated
        - Use should be limited to 12 monthly doses

- **AEs**
    - Bisphosphonates
        - The most common AEs are headache and GI effects such as abdominal pain, diarrhea, constipation, nausea, and dyspepsia.
    - Raloxifene
        - The most common AEs (> 2%) include hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating.
    - Teriparatide
        - The most common AEs (> 10%) include nausea, arthralgia, and pain.
    - Abaloparatide
        - The most common AEs (≥ 2%) include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.
    - Recombinant parathyroid hormone
        - The most common AEs (> 10%) include paresthesia, hypocalcemia, headache, hypercalcemia, hypoaesthesia, diarrhea, vomiting, arthralgia, nausea, hypercalciuria, and extremity pain.
    - Calcitonin
        - Nasal spray: The most common AEs (≥ 3%) include rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache.
        - Injection: The most common AEs include nausea with or without vomiting (10%), injection site inflammation (10%), and flushing of the face or hands (2 to 5%).
    - Denosumab
        - The most common AEs (> 5%) include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, cystitis, nasopharyngitis, bronchitis, and headache. Pancreatitis has also been reported in clinical trials.
    - Romosozumab
        - The most common AEs (≥ 5%) include arthralgia and headache.

- **Drug Interactions**
    - Bisphosphonates

        - Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with absorption of oral bisphosphonates
        - Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) increase GI AEs with oral bisphosphonates
        - Olestra, mineral oils, orlistat and bile acid sequestrants may impair the absorption of vitamin D (alendronate/cholecalciferol).
    - Raloxifene
        - Cholestyramine, warfarin, highly protein-bound drugs, ampicillin, and amoxicillin.
    - Teriparatide and recombinant parathyroid hormone
        - Hypercalcemia may predispose patients to digitalis toxicity; caution recommended in patients on digoxin
    - Calcitonin
        - Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations

- **Risk Evaluation and Mitigation Strategy (REMS)**
    - Denosumab has a REMS program with the goal of mitigating the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions (*REMS Website 2020*).
        - The REMS program includes a medication guide and a communication plan to healthcare providers who prescribe denosumab.
    - Recombinant parathyroid hormone has a REMS program with the goal of increasing awareness and mitigating the risk of osteosarcoma *(REMS Website 2020).*
        - All prescribers and dispensing pharmacies must be certified through the REMS program.

DOSING AND ADMINISTRATION

- Bisphosphonates
    - Oral bisphosphonates should be taken at least 30 minutes (60 minutes for ibandronate) before the first food or drink of the day and swallowed whole in an upright position and with a full glass of plain water. Patients should not lie down for 30 minutes (60 minutes for ibandronate) after ingestion.
        - Exception: Delayed-release risedronate should be taken immediately after breakfast
    - Supplemental calcium and vitamin D are recommended if dietary intake is inadequate; however, calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with bisphosphonate absorption and should be administered at a different time of the day.
- Calcitonin
    - Unopened nasal spray bottle should be stored in the refrigerator. Once opened, it should be stored at room temperature and discarded after 35 days.
    - Injection should be stored in the refrigerator. If the volume of the injection exceeds 2 mL, intramuscular (IM) injection is preferable, and the total dose should be distributed across multiple injection sites.
- Parathyroid Hormone Analogs
    - Teriparatide prefilled pens should be refrigerated at all times and injected into the thigh or abdominal wall.
    - Abaloparatide prefilled pens should be refrigerated before use then stored at room temperature for up to 30 days after first use. The injection should be into the periumbilical region of abdomen at approximately the same time every day.
    - Recombinant parathyroid hormone must be reconstituted prior to administration using a mixing device and should be administered using the Q-Cliq pen delivery device into the thigh, rotating thighs each day. Reconstituted parathyroid hormone should be stored in the Q-Cliq pen device in the refrigerator for no more than 14 days.
- Denosumab
    - Denosumab should be administered by a healthcare professional in the upper arm, upper thigh, or abdomen.
- Romosozumab
    - Romosozumab should be administered by a healthcare professional as 2 separate injections, one after the other in the upper arm, thigh, or abdomen.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Bisphosphonates			

Drug	Available Formulations	Route	Usual Recommended Frequency
Actonel (risedronate)	Tablets	Oral	Once daily Once weekly Once monthly
Atelvia (risedronate)	Delayed release tablets	Oral	Once weekly
Binosto (alendronate)	Effervescent tablets	Oral	Once weekly
Boniva (ibandronate)	Tablets Injection	Oral IV	Once monthly (oral) Every 3 months (IV)
Didronel (etidronate)	Tablets	Oral	Once daily (for osteoporosis and Paget's disease)
Fosamax (alendronate)	Tablets Solution	Oral	Once daily Once weekly
Fosamax Plus D (alendronate/ cholecalciferol)	Tablets	Oral	Once weekly
Reclast (zoledronic acid)	Injection	IV	Once a year (treatment) Once every 2 years (prevention)
Calcitonin			
Miacalcin (calcitonin-salmon synthetic)	Nasal solution Injection	Intranasal SQ, IM	Once daily (for osteoporosis and Paget's disease)
Estrogen Agonist-Antagonist			
Evista (raloxifene)	Tablets	Oral	Once daily
Parathyroid Hormone Analogs			
Forteo, Bonsity (teriparatide)	Injection	SQ	Once daily
Natpara (recombinant parathyroid hormone)	Injection	SQ	Once daily
Tymlos (abaloparatide)	Injection	SQ	Once daily
Receptor Activator of Nuclear Factor K-B Ligand Inhibitors			
Prolia (denosumab)	Injection	SQ	Every 6 months
Sclerostin Inhibitor			
Evenity (romosozumab)	Injection	SQ	Once monthly

Abbreviations: IM = intramuscular; IV = intravenous; SQ = subcutaneous

See the current prescribing information for full details

CONCLUSION

- Within the various treatment guidelines for osteoporosis in men and women, there is general agreement that treatment is indicated for patients > 50 years of age who have experienced a hip or vertebral fracture or have a bone density T-score ≤ -2.5 (*Adler et al 2016, Camacho et al 2016, Conley et al 2020, Cosman et al 2014, Eastell et al 2019, Ketteler et al, 2018, North American Menopause Society 2010, Qaseem et al 2017, Watts et al 2012*). Bisphosphonates are generally considered first-line therapy, and clinical trials have not consistently shown one agent to be more effective than another.
- Data for hip, vertebral, and nonvertebral fractures are most robust for alendronate, risedronate, and zoledronic acid. Ibandronate has data to support reduced vertebral fractures (*Guanabens et al 2013, Harris et al 2009, Miller et al 2008[a]*).
- Patient preference and ease of administration should be considered in the selection of a bisphosphonate, as adherence may be a barrier to the treatment and prevention of osteoporosis. Atelvia (risedronate delayed release) and alendronate can be administered once weekly, while Actonel (risedronate) and ibandronate can be administered once a month. Additionally, zoledronic acid is an intravenous infusion given once a year for treatment or every other year for prevention. Atelvia (risedronate delayed release) can be taken immediately after eating or drinking while other oral bisphosphonates must be administered 30 to 60 minutes before the first food or drink of the day.

- The receptor activator of nuclear factor K-B ligand inhibitor, denosumab, has data for hip, vertebral, and nonvertebral fractures. It is a subcutaneous injection given every six months. Monitoring for infection is required with this agent. The AACE recommends denosumab as an optional first-line treatment for postmenopausal osteoporosis (*Camacho et al 2016*) or as an option for patients who cannot take oral bisphosphonates (*Conley et al 2020*)
- Teriparatide and abaloparatide are generally reserved for patients at high risk for fractures (*Conley et al 2020*) or those unable to tolerate or manage therapy with oral bisphosphonates (*ACOG 2012, Camacho et al 2016, Eastell et al 2019, Watts et al 2012*). Both teriparatide and abaloparatide are administered via daily subcutaneous injection, and lifetime cumulative treatment duration should not exceed 2 years. The parathyroid hormone analogs have a boxed warning for osteosarcoma.
- Romosozumab is the newest agent approved for the treatment of osteoporosis in postmenopausal women at high risk of fracture and in patients who have failed or are intolerant to other therapies, and it has not yet been incorporated into treatment guidelines. It is administered as a monthly subcutaneous injection for no more than 12 months.
- Raloxifene has data for vertebral fracture reduction and is only approved for women. It may be an appropriate initial therapy for patients requiring drugs with spine-specific efficacy who are unable to tolerate bisphosphonates (*Camacho et al 2016*). Raloxifene is also used for breast cancer risk reduction, which is recommended for asymptomatic women ≥ 35 years of age who are at risk for breast cancer. There is an increased risk of thromboembolism and stroke with raloxifene.
- The ASBMR 2020 guideline mentions anabolic therapy such as romosozumab as an option in patients at high risk of secondary fracture; particularly those with a previous vertebral fracture (Conley et al 2020).
- Calcitonin lacks sufficient evidence for fracture reduction in the treatment of osteoporosis.
- For the treatment of Paget's disease, risedronate, alendronate, etidronate, calcitonin injection, and zoledronic acid all have efficacy data to support their use.
- For the treatment of glucocorticoid-induced osteoporosis, risedronate, teriparatide, alendronate, denosumab, and zoledronic acid are all FDA-approved. Selection of an agent should be based on the patient's preference of administration. Oral bisphosphonates are preferred. If these cannot be used, the agents recommended in order of preference are IV bisphosphonates, teriparatide, and then denosumab (*Buckley et al 2017*).

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Publication Date: February 19, 2020

Board Requested Reports

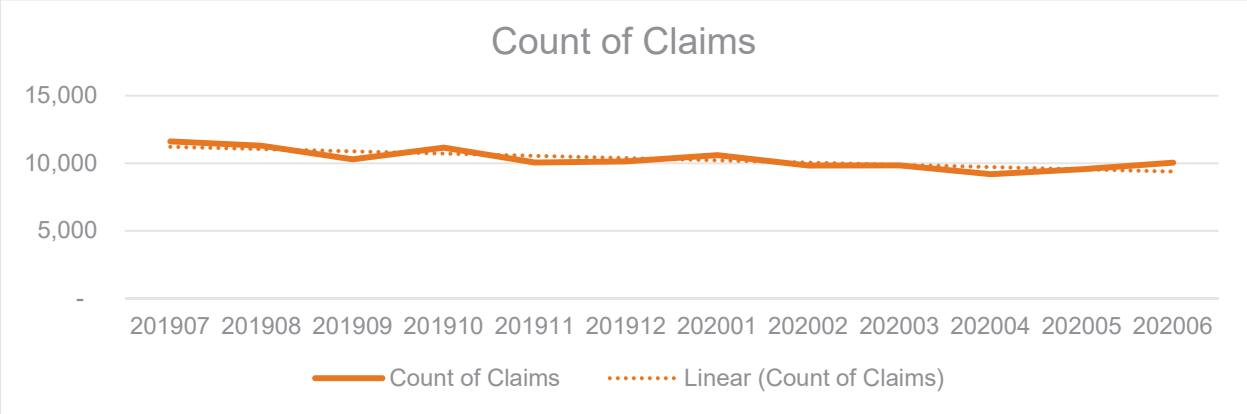
Nevada Medicaid

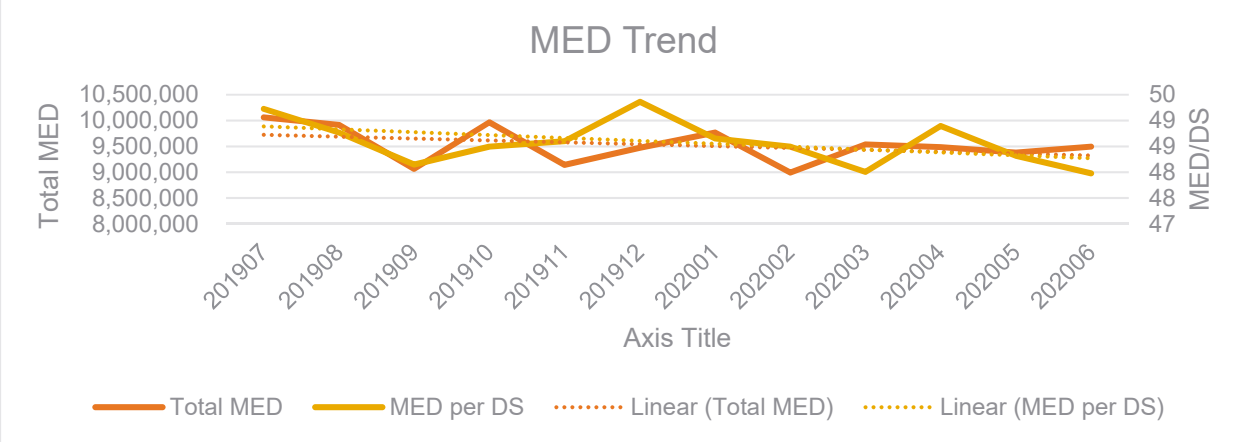
Opioid Trends

Fee for Service

July 1, 2019 – June 30, 2020

Date Filled	Count of Claims	Total MED	Days Supply	Count of Members	MED per DS
201907	11,617	10,061,714	204,395	9,832	49
201908	11,296	9,917,493	203,360	9,688	49
201909	10,294	9,064,245	188,255	9,110	48
201910	11,163	9,966,381	205,513	9,601	48
201911	10,055	9,143,067	188,125	8,874	49
201912	10,136	9,475,265	191,948	8,830	49
202001	10,598	9,767,494	200,762	9,179	49
202002	9,834	8,993,690	185,459	8,749	48
202003	9,840	9,539,999	198,724	8,549	48
202004	9,190	9,485,990	194,008	8,030	49
202005	9,553	9,380,390	194,132	8,366	48
202006	10,040	9,494,872	197,900	8,761	48





Nevada Medicaid

Opioid Trends – Top Ten Members

Fee for Service

April 1, 2020 – June 30, 2020

Member ID Encrypted	Count of Claims	Days Supply	Total Quantity	Total MED
77771952964	9	270	1,080	89,100
22222296971	6	160	780	64,800
44448546720	7	210	1,590	62,100
33330458115	6	180	1,080	57,600
44446597311	6	180	750	54,000
11110100737	9	254	1,530	48,600
76050522223	6	180	720	45,900
49044066667	6	168	924	45,360
66667788323	9	270	990	44,550
77771924497	6	180	630	43,200
71367188889	6	180	630	43,200

Member ID Encrypted	Drug Label Name	Count of Claims	Total Days Supply	Total Quantity
11110100737	OXYCODONE TAB 10MG	1	28	120
11110100737	MORPHINE SUL TAB 100MG ER	3	84	360
11110100737	OXYCODONE TAB 30MG	2	58	240
11110100737	METHADONE TAB 10MG	3	84	810
22222296971	FENTANYL DIS 75MCG/HR	3	70	60
22222296971	OXYCODONE TAB 30MG	3	90	720
33330458115	OXYCODONE TAB 20MG	3	90	720
33330458115	MORPHINE SUL TAB 100MG ER	3	90	360
44446597311	OXYCODONE TAB 30MG	4	120	720
44446597311	FENTANYL DIS 100MCG/H	2	60	30
44448546720	OXYCODONE TAB 30MG	4	120	1,320
44448546720	HYDROCO/APAP TAB 10-325MG	3	90	270
49044066667	MORPHINE SUL TAB 60MG ER	3	84	252
49044066667	OXYCODONE TAB 30MG	3	84	672
66667788323	MORPHINE SUL TAB 30MG ER	3	90	270
66667788323	MORPHINE SUL TAB 60MG ER	3	90	270
66667788323	OXYCODONE TAB 30MG	3	90	450
71367188889	MORPHINE SUL TAB 100MG ER	3	90	270
71367188889	OXYCODONE TAB 30MG	3	90	360
76050522223	OXYCODONE TAB 30MG	3	90	540
76050522223	OXYCONTIN TAB 80MG CR	3	90	180
77771924497	OXYCODONE TAB 30MG	3	90	360
77771924497	MORPHINE SUL TAB 100MG ER	3	90	270
77771952964	OXYCODONE TAB 30MG	3	90	540
77771952964	METHADONE TAB 10MG	3	90	450
77771952964	FENTANYL DIS 100MCG/H	3	90	90

Nevada Medicaid

Fee for Service - Opioid Trends – Top Ten Prescribers

By Morphine Equivalent Dose (MED)

Quarter Filled	Prescriber	City	Degree	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Quantity	Total MED	MED/ DS	MED/ DS/ Member
2020 Q2	A	RENO	DO	Anesthesiology	152	401	12,083	50,207	661,678	54.8	0.36
2020 Q2	B	SPARKS	MD	Anesthesiology	96	242	7,141	20,623	536,968	75.2	0.78
2020 Q2	C	LAS VEGAS			173	365	10,816	35,909	525,503	48.6	0.28
2020 Q2	D	LAS VEGAS	PAC	Physician Assistant	84	230	6,570	22,012	480,426	73.1	0.87
2020 Q2	E	LAS VEGAS			136	316	8,612	27,601	468,339	54.4	0.40
2020 Q2	F	LAS VEGAS	NP	Nurse Practitioner	119	243	7,195	21,609	426,363	59.3	0.50
2020 Q2	G	HENDERSON	PAC	Physician Assistant	38	92	2,665	10,140	416,700	156.4	4.11
2020 Q2	H	LAS VEGAS			133	313	9,063	30,664	411,833	45.4	0.34
2020 Q2	I	HENDERSON	MS	Nurse Practitioner	85	171	4,582	15,750	376,881	82.3	0.97
2020 Q2	J	HENDERSON	PAC	Physician Assistants	73	194	5,819	20,460	366,330	63.0	0.86
2020 Q1	A	RENO	DO	Anesthesiology	164	404	11,644	48,067	643,691	55.3	0.34
2020 Q1	C	LAS VEGAS			201	404	11,675	38,286	570,341	48.9	0.24
2020 Q1	E	LAS VEGAS			153	365	10,162	32,984	566,903	55.8	0.36
2020 Q1	B	SPARKS	MD	Anesthesiology	93	230	6,769	19,320	496,876	73.4	0.79
2020 Q1	D	LAS VEGAS	PAC	Physician Assistant	87	227	6,370	21,131	468,064	73.5	0.84
2020 Q1	F	LAS VEGAS	NP	Nurse Practitioner	115	242	7,169	21,696	458,874	64.0	0.56
2020 Q1	H	LAS VEGAS			131	301	8,781	29,857	392,942	44.7	0.34
2020 Q1	J	HENDERSON	PAC	Physician Assistants	81	205	6,135	22,240	389,168	63.4	0.78
2020 Q1	I	HENDERSON	MS	Nurse Practitioner	94	170	4,542	15,396	387,643	85.3	0.91
2020 Q1	G	HENDERSON	PAC	Physician Assistant	35	80	2,315	9,010	381,900	165.0	4.71

By Morphine Equivalent Dose (MED) Per Member Per Day Supply

Quarter filled	Prescriber	City	Degree	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Quantity	Total MED	MED/DS	MED/ DS/ Member
2020 Q2	K	LAS VEGAS	PAC	Physician Assistant	1	1	5	30	1,350	270.0	270.00
2020 Q2	L	LAS VEGAS	MD	Anesthesiology	1	1	30	150	6,750	225.0	225.00
2020 Q2	M	Reed City, MI	PAC	Physician Assistant	1	1	15	5	2,700	180.0	180.00
2020 Q2	N	LAS VEGAS	DO	Family Medicine	1	1	30	120	5,400	180.0	180.00
2020 Q2	O	CARSON CITY	MD	Family Medicine	1	3	90	360	16,200	180.0	180.00
2020 Q2	P	Salt Lake City	MD	Anesthesiology	1	1	15	5	2,700	180.0	180.00
2020 Q2	Q	Salt Lake City	NP	Nurse Practitioner	1	1	4	40	600	150.0	150.00
2020 Q2	R	LAS VEGAS	MD	Specialist	2	6	180	1,110	49,950	277.5	138.75
2020 Q2	S	Salt Lake City	MD	Anesthesiology	2	3	60	195	16,200	270.0	135.00
2020 Q2	T	LAS VEGAS	MD	Internal Medicine	1	2	60	180	8,100	135.0	135.00
2020 Q1	U	LAS VEGAS	MD	Internal Medicine	1	1	30	240	10,800	360.0	360.00
2020 Q1	V	LAS VEGAS	MD	Internal Medicine	1	2	40	240	10,800	270.0	270.00
2020 Q1	W	Twin Falls	MD	Ortho Surgery	1	1	5	60	900	180.0	180.00
2020 Q1	X	San Angelo, TX	MD	Family Medicine	1	1	30	120	5,400	180.0	180.00
2020 Q1	Y	LAS VEGAS	MD	Internal Medicine	1	1	30	120	5,400	180.0	180.00
2020 Q1	Z	Payette, ID	PAC	Physician Assistant	1	8	43	420	6,300	146.5	146.51
2020 Q1	T	LAS VEGAS	MD	Internal Medicine	1	3	90	270	12,150	135.0	135.00
2020 Q1	AA	LAS VEGAS	PB	Physician Assistant	1	1	30	180	4,050	135.0	135.00
2020 Q1	BB	CARSON CITY	MD	Family Medicine	1	1	30	90	4,050	135.0	135.00
2020 Q1	CC	RENO	MD	Internal Medicine	1	1	30	180	4,050	135.0	135.00

Nevada Medicaid

Opioid and Benzodiazepine Combos

Fee for Service

July 1, 2019 – June 30, 2020

Members on an Opioid

Quarter	Count of Members
2019 Q3	12,919
2019 Q4	12,368
2020 Q1	11,884
2020 Q2	10,956
Total	233,583

Members on a Benzo

Quarter	Count of Members
2019 Q3	5,029
2019 Q4	4,627
2020 Q1	4,507
2020 Q2	4,352
Total	9,823

Members on both Opioid and Benzo

Quarter	Count of Members
2019 Q3	2,892
2019 Q4	2,695
2020 Q1	2,502
2020 Q2	2,379
Total	4,319

Top Ten Products Used by Quarter

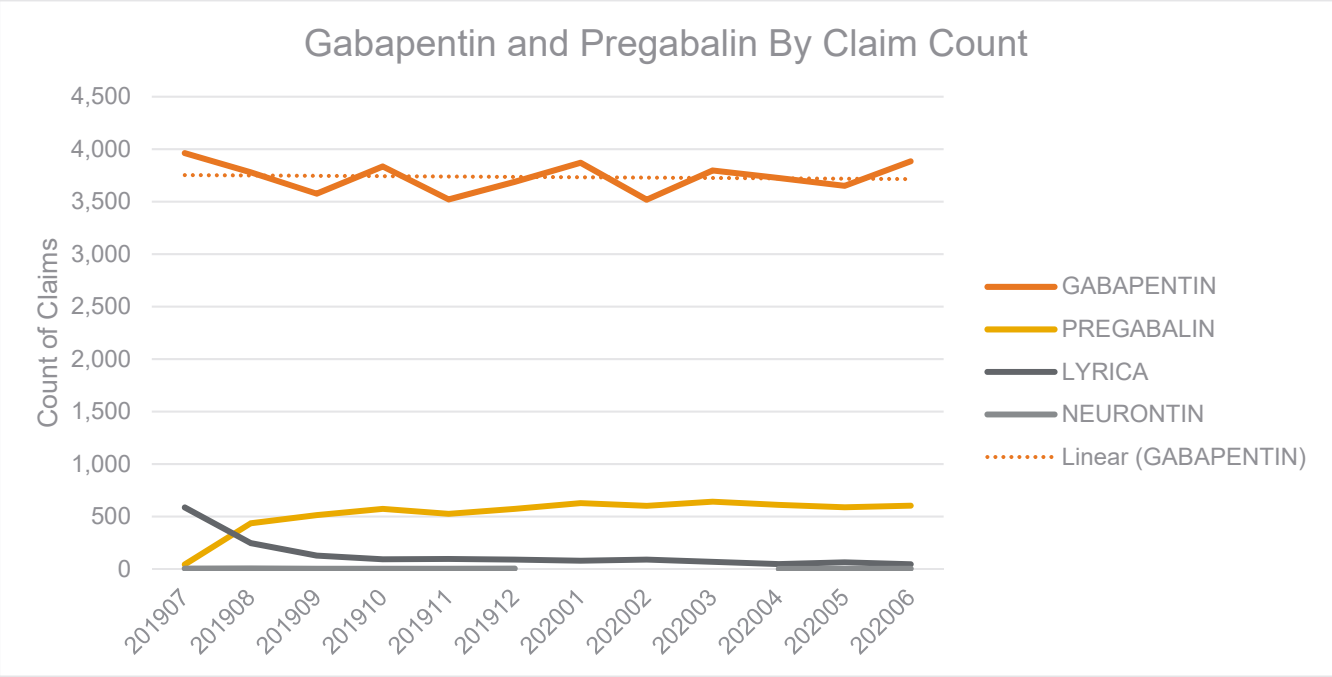
Quarter filled	Drug Label Name	Count of Members	Quarter filled	Drug Label Name	Count of Members
	Opioids			**Benzodiazepines**	
2020 Q2	HYDROCO/APAP TAB 10-325MG	645	**2020 Q2**	ALPRAZOLAM TAB 1MG	703
2020 Q2	OXYCOD/APAP TAB 10-325MG	478	**2020 Q2**	ALPRAZOLAM TAB 0.5MG	627
2020 Q2	HYDROCO/APAP TAB 5-325MG	415	**2020 Q2**	DIAZEPAM TAB 5MG	588
2020 Q2	TRAMADOL HCL TAB 50MG	326	**2020 Q2**	LORAZEPAM INJ 2MG/ML	421
2020 Q2	OXYCODONE TAB 10MG	211	**2020 Q2**	ALPRAZOLAM TAB 2MG	404
2020 Q2	OXYCOD/APAP TAB 5-325MG	190	**2020 Q2**	LORAZEPAM TAB 1MG	365
2020 Q2	HYDROCO/APAP TAB 7.5-325	165	**2020 Q2**	DIAZEPAM TAB 10MG	333
2020 Q2	OXYCODONE TAB 15MG	160	**2020 Q2**	LORAZEPAM TAB 0.5MG	255
2020 Q2	OXYCODONE TAB 30MG	159	**2020 Q2**	ALPRAZOLAM TAB 0.25MG	233
2020 Q2	MORPHINE SUL TAB 15MG ER	158	**2020 Q2**	DIAZEPAM TAB 2MG	71

2020 Q1	HYDROCO/APAP TAB 10-325MG	664	**2020 Q1**	ALPRAZOLAM TAB 1MG	740
2020 Q1	HYDROCO/APAP TAB 5-325MG	505	**2020 Q1**	ALPRAZOLAM TAB 0.5MG	677
2020 Q1	OXYCOD/APAP TAB 10-325MG	475	**2020 Q1**	DIAZEPAM TAB 5MG	651
2020 Q1	TRAMADOL HCL TAB 50MG	344	**2020 Q1**	LORAZEPAM INJ 2MG/ML	510
2020 Q1	OXYCOD/APAP TAB 5-325MG	248	**2020 Q1**	ALPRAZOLAM TAB 2MG	405
2020 Q1	OXYCODONE TAB 10MG	232	**2020 Q1**	LORAZEPAM TAB 1MG	378
2020 Q1	HYDROCO/APAP TAB 7.5-325	198	**2020 Q1**	DIAZEPAM TAB 10MG	347
2020 Q1	MORPHINE SUL INJ 4MG/ML	183	**2020 Q1**	ALPRAZOLAM TAB 0.25MG	269
2020 Q1	OXYCODONE TAB 15MG	173	**2020 Q1**	LORAZEPAM TAB 0.5MG	256
2020 Q1	OXYCODONE TAB 30MG	158	**2020 Q1**	DIAZEPAM TAB 2MG	80
2019 Q4	HYDROCO/APAP TAB 10-325MG	693	**2019 Q4**	ALPRAZOLAM TAB 1MG	760
2019 Q4	HYDROCO/APAP TAB 5-325MG	578	**2019 Q4**	ALPRAZOLAM TAB 0.5MG	729
2019 Q4	OXYCOD/APAP TAB 10-325MG	507	**2019 Q4**	DIAZEPAM TAB 5MG	714
2019 Q4	TRAMADOL HCL TAB 50MG	388	**2019 Q4**	LORAZEPAM INJ 2MG/ML	699
2019 Q4	MORPHINE SUL INJ 4MG/ML	372	**2019 Q4**	LORAZEPAM TAB 1MG	498
2019 Q4	OXYCOD/APAP TAB 5-325MG	259	**2019 Q4**	ALPRAZOLAM TAB 2MG	436
2019 Q4	OXYCODONE TAB 10MG	222	**2019 Q4**	DIAZEPAM TAB 10MG	373
2019 Q4	HYDROCO/APAP TAB 7.5-325	216	**2019 Q4**	ALPRAZOLAM TAB 0.25MG	291
2019 Q4	OXYCODONE TAB 15MG	183	**2019 Q4**	LORAZEPAM TAB 0.5MG	271
2019 Q4	OXYCODONE TAB 30MG	171	**2019 Q4**	DIAZEPAM TAB 2MG	86
2019 Q3	HYDROCO/APAP TAB 10-325MG	750	**2019 Q3**	LORAZEPAM INJ 2MG/ML	924
2019 Q3	HYDROCO/APAP TAB 5-325MG	702	**2019 Q3**	ALPRAZOLAM TAB 1MG	892
2019 Q3	MORPHINE SUL INJ 4MG/ML	671	**2019 Q3**	DIAZEPAM TAB 5MG	829
2019 Q3	OXYCOD/APAP TAB 10-325MG	506	**2019 Q3**	ALPRAZOLAM TAB 0.5MG	821
2019 Q3	TRAMADOL HCL TAB 50MG	403	**2019 Q3**	LORAZEPAM TAB 1MG	587
2019 Q3	HYDROCO/APAP TAB 7.5-325	269	**2019 Q3**	ALPRAZOLAM TAB 2MG	527
2019 Q3	OXYCOD/APAP TAB 5-325MG	247	**2019 Q3**	DIAZEPAM TAB 10MG	405
2019 Q3	OXYCODONE TAB 10MG	234	**2019 Q3**	ALPRAZOLAM TAB 0.25MG	356
2019 Q3	HYDROMORPHON INJ 1MG/ML	214	**2019 Q3**	LORAZEPAM TAB 0.5MG	315
2019 Q3	OXYCODONE TAB 15MG	198	**2019 Q3**	DIAZEPAM TAB 2MG	100

Nevada Medicaid
Gabapentin and Pregabalin
Fee for Service
July 1, 2019 – June 30, 2020

Date Filled YYYYMM	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
201907	NEURONTIN	5	5	76	365
201907	GABAPENTIN	3,283	3,963	124,095	394,264.333
201907	LYRICA	520	587	16,053	40,109
201907	PREGABALIN	43	44	1,543	3,866
201908	GABAPENTIN	3,224	3,780	122,081	386,908.2
201908	NEURONTIN	5	6	173	913
201908	PREGABALIN	403	436	12,752	31,519
201908	LYRICA	181	248	5,249	12,676
201909	NEURONTIN	3	4	82	192
201909	GABAPENTIN	3,109	3,577	111,021	354,866
201909	LYRICA	101	128	2,493	6,215.12
201909	PREGABALIN	453	514	14,769	36,528
201910	NEURONTIN	4	4	33	96
201910	GABAPENTIN	3,279	3,835	124,316	395,662
201910	PREGABALIN	516	574	16,979	42,283
201910	LYRICA	79	94	1,892	4,913
201911	GABAPENTIN	3,040	3,521	109,858	351,288.25
201911	NEURONTIN	4	4	93	725
201911	LYRICA	80	96	1,982	5,024
201911	PREGABALIN	476	526	15,158	37,946
201912	GABAPENTIN	3,142	3,689	117,947	377,173
201912	NEURONTIN	4	5	34	96
201912	PREGABALIN	509	574	16,272	40,278.5
201912	LYRICA	70	90	1,542	3,873
202001	GABAPENTIN	3,327	3,871	126,127	399,287
202001	LYRICA	63	80	1,395	3,400
202001	PREGABALIN	556	629	17,845	43,374
202002	NEURONTIN	2	2	120	810
202002	GABAPENTIN	3,087	3,519	112,191	355,783
202002	LYRICA	64	90	1,323	3,346
202002	PREGABALIN	527	602	16,569	40,974
202003	GABAPENTIN	3,200	3,798	124,780	394,657.1
202003	LYRICA	53	69	1,010	2,467
202003	PREGABALIN	554	642	17,999	45,276
202004	GABAPENTIN	3,235	3,726	123,475	394,487
202004	NEURONTIN	1	1	30	90
202004	LYRICA	41	48	1,096	2,640
202004	PREGABALIN	554	611	17,945	45,008
202005	GABAPENTIN	3,162	3,651	120,956	387,287
202005	NEURONTIN	2	2	120	810
202005	PREGABALIN	525	589	16,848	42,749
202005	LYRICA	44	65	1,103	2,769

	202006	GABAPENTIN	3,328	3,885	130,192	406,826
	202006	NEURONTIN	2	3	32	150
	202006	LYRICA	41	46	965	2,334
	202006	PREGABALIN	541	604	17,951	45,038



Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

January 1, 2020 – June 30, 2020

Drug Class	Count of Claims	Amt Paid	Drug Class	Count of Claims	Amt Paid
2020 Q2 - Top 10 Classes by Claim Count			**2020 Q1 - Top 10 Classes by Claim Count**		
ANTICONVULSANTS - MISC.	26,955	$2,584,579.46	ANTICONVULSANTS - MISC.	26,905	$2,548,542.10
SYMPATHOMIMETICS	18,080	$2,679,728.72	SYMPATHOMIMETICS	20,963	$2,808,141.58
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,126	$207,453.85	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,398	$213,391.12
OPIOID COMBINATIONS	15,054	$418,249.28	OPIOID COMBINATIONS	15,041	$362,389.90
CENTRAL MUSCLE RELAXANTS	12,680	$217,094.95	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	14,490	$308,559.80
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	12,495	$289,764.20	CENTRAL MUSCLE RELAXANTS	12,619	$220,373.99
HMG COA REDUCTASE INHIBITORS	10,772	$342,336.70	HMG COA REDUCTASE INHIBITORS	10,731	$344,670.30
DIBENZAPINES	10,008	$349,903.08	DIBENZAPINES	10,093	$388,339.57
OPIOID AGONISTS	9,824	$556,463.59	OPIOID AGONISTS	9,918	$558,804.60
ANTIANXIETY AGENTS - MISC.	9,188	$142,173.21	ANTIANXIETY AGENTS - MISC.	8,667	$132,599.92

Drug Class	Count of Claims	Amt Paid	Drug Class	Count of Claims	Amt Paid
2020 Q2 - Top 10 Classes by Amount Paid			**2020 Q1 - Top 10 Classes by Amount Paid**		
ANTIHEMOPHILIC PRODUCTS	105	$13,082,576.52	ANTIHEMOPHILIC PRODUCTS	113	$13,210,390.71
ANTIRETROVIRALS	1,823	$3,966,890.01	ANTIRETROVIRALS	1,902	$3,772,714.82
INSULIN	4,829	$3,388,993.43	INSULIN	4,935	$3,434,268.19
LOCAL ANESTHETICS - TOPICAL	1,999	$3,104,137.04	SYMPATHOMIMETICS	20,963	$2,808,141.58
SYMPATHOMIMETICS	18,080	$2,679,728.72	LOCAL ANESTHETICS - TOPICAL	1,751	$2,591,835.47
ANTIPSYCHOTICS - MISC.	3,047	$2,615,121.33	ANTICONVULSANTS - MISC.	26,905	$2,548,542.10
ANTICONVULSANTS - MISC.	26,955	$2,584,579.46	BENZISOXAZOLES	5,809	$2,499,793.81
BENZISOXAZOLES	5,881	$2,566,864.82	ANTIPSYCHOTICS - MISC.	3,032	$2,451,959.51
ANTINEOPLASTIC ENZYME INHIBITORS	178	$2,088,167.72	QUINOLINONE DERIVATIVES	5,085	$1,907,790.08
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	293	$2,079,590.17	ANTINEOPLASTIC ENZYME INHIBITORS	160	$1,863,515.08

cDUR Quarterly Report

Client(s): 'NVM'
Carrier ID: NVM
Account(s): All
Group(s): All
Primary Start Date: April 1, 2020
Primary End Date: June 30, 2020

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	603,622	140,136	23.2%
Rejected	484,905	170,902	35.2%
Reversed	98,907	33,026	33.4%
Total	***1,187,434***	***344,064***	***29.0%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
44,408	**$5,058,750**	**25,443**	**$10,049,290**	**69,851**	**$15,108,040**	**114,480**	**$38,352,851**

cDUR Detailed Activity Summary:

Intervention Type	Total	Paid Rxs		Rejected Rxs		Reversed Rxs	
	Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions
Dosing/Duration (DOSECHEK)	41,677	32,430	77.8%	933	2.2%	8,314	19.9%
Drug-Drug Interaction (DDI-DTMS)	119,692	54,647	45.7%	57,251	47.8%	7,794	6.5%
Duplicate Therapy (DUPTHER)	98,040	43,009	43.9%	46,412	47.3%	8,619	8.8%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	21	12	57.1%	N/A	N/A	9	42.9%
Duplicate Rx (DUPRX)	84,127	10,013	11.9%	65,871	78.3%	8,243	9.8%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	56	12	21.4%	N/A	N/A	44	78.6%
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	16	13	81.3%	N/A	N/A	3	18.8%
Refill Too Soon	435	N/A	N/A	435	100.0%	N/A	N/A
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***344,064***	***140,136***	***40.7%***	***170,902***	***49.7%***	***33,026***	***9.6%***

cDUR Detailed Saving Outcomes Summary:

Intervention Type	Current		Accruing		Total		Total Year to Date	
	Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
Dosing/Duration (DOSECHEK)	1,153	$974,325	2,105	$4,685,238	3,258	$5,659,563	4,957	$19,024,964
Drug-Drug Interaction (DDI-DTMS)	3,382	$313,917	5,321	$993,457	8,703	$1,307,374	13,815	$2,814,441
Duplicate Therapy (DUPTHER)	4,477	$1,086,741	9,555	$3,220,694	14,032	$4,307,435	19,014	$8,490,076
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	0	$0	0	$0	0	$0	3	$14
Duplicate Rx (DUPRX)	34,993	$2,661,042	8,351	$1,133,663	43,344	$3,794,705	75,059	$7,855,741
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	37	$509	N/A	N/A	37	$509	37	$509
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	2	$376	0	$0	2	$376	14	$2,554
Refill Too Soon	364	$21,840	111	$16,238	475	$38,078	1,581	$164,551
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***44,408***	***$5,058,750***	***25,443***	***$10,049,290***	***69,851***	***$15,108,040***	***114,480***	***$38,352,851***

Claims Summary:

Column Name	Description
Claim Status	The claims status associated with the RxCLAIM transaction: Paid, Reversed, Rejected •Paid Claims with CDUR edit(s) are those which had an override by a pharmacist •Rejected claims with CDUR edit(s) include both hard and soft rejects •Reversed claims with CDUR edit(s) include Paid claims which were reversed, originating with a message and an override by a pharmacist
Total Rxs	The total number of pharmacy claims with or without a cDUR edit
Total Interventions	The total number of pharmacy claims with at least one cDUR edit
% Total Rxs w/ Interventions	Percentage of all pharmacy claims which had a cDUR edit

cDUR Savings Outcomes Summary:

Column Name	Description
Current	Savings from CDUR interventions which occurred in the current period
Accruing	Savings from CDUR interventions which succeeded prior to the current reporting period, where savings continue to accrue in the current reporting period
Total	Total CDUR savings recognized in the current period (Current + Accruing)
Year To Date	Total CDUR savings recognized since the start of the current year
Successes	cDUR Interventions which resulted in Pharmacy Savings in the Current Period

Edit Type	Short Description	Long Description
ACTMAINT	Acute/Maintenance Dose Screening	Member is taking a medication at a higher dose than recommended based on acute daily use versus maintenance daily use.
ALLERCHK	Drug-Allergy Interaction Screening	Member is taking a medication to which he/she may be allergic.
DDI-DTMS	Drug-Drug Interaction Screening	Member is taking 2 interacting medications and/or medication classes.
DIAGCAUT	Drug-Disease screening using actual member disease profile	Member has a certain diagnosis (as determined by member disease profile) and is taking a medication that worsens the diagnosis.
DINFERRD	Drug-Disease screening using medication history as proxy for determining existing disease states	Member has a certain diagnosis (as determined by drug proxy) and is taking a medication that may worsen the member diagnosis.
DOSECHEK	Identifies if incoming claim exceeds recommended daily dose and/or recommended duration	Member is taking a medication for longer and/or at a higher dose than recommended.
DRUG_AGE	Drug-Age contraindication screening	Member is taking a medication that is not recommended for people of certain ages (pediatric and geriatric).
DRUG_SEX	Drug-sex contraindication screening	Member is taking a medication that is not recommended for his/her gender.
DUPRX	Exact GPI duplication screening	Member is taking 2 medications with the same ingredient.
DUPTHER	Drug class duplication screening	Member is taking 2 medications in the same drug class.
MEDLIMIT	Morphine Equivalent Dose Limit Screening	Member is taking opioids where the total cumulative daily dose exceeds the suggested morphine equivalent dose (MED).
REFILL	Refill Too Soon	Member tried refilling with medicagtion still left of hand from prior fill
THERDOSE	Therapeutic Dose Limits Screening	Member is taking medications where the total cumulative daily dose exceeds the FDA approved maximum dose for the medication.

Nevada Medicaid
RetroDUR
Fee for Service
January 1, 2020 – June 30, 2020

Initiative	Letters Sent	Responses	Prescribers	Recipients	Response Rate
Q3 2019					
Diabetes without Statin	73	5	65	61	6.85%
Albuterol wo Long Term Control Meds	90	3	70	90	3.33%
Q4 2019					
Triptan w Preventative	31	7	29	31	22.58%
Hep C Treatment Completed	149	46	53	149	30.87%
Q1 2020					
Zolpidem	40	9	40	40	22.50%
Q2 2020					
COPD	27	4	26	27	14.81%