Nevada Medicaid Drug Use Review Board Meeting

January 23, 2020

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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	December 12, 2019
Date of Meeting:	January 23, 2020 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).
Place of Meeting:	Hyatt Place Reno -Tahoe Airport 1790 E. Plumb Lane Reno, Nevada 89502 Phone: (775) 826-2500
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e260d768575d927135883a3960784adbd Or go to www.webex.com and enter the Event Number listed below. Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.
Event Number:	646 050 877 Click "Join Now" Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. A password should not be necessary, but if asked use: Medicaid1! For Audio Only: Phone: (763) 957-6300 Event: 646 050 877

AGENDA

1. Call to Order and Roll Call

2. Public Comment on Any Matter on the Agenda

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from October 17, 2019

b. **Status Update by DHCFP**

1. MSM Chapter 1200 policy update regarding recommendations from the July 25, 2019 DUR Board meeting.
2. Addition of HHS resource link on Guide for Clinicians on the Appropriate Dosage, Reduction or Discontinuation of Long-Term Opioid Analgesics to the DHCFP Pharmacy web site, http://dhcfp.nv.gov/Pgms/CPT/Pharmacy/.
3. Update on diabetic supply/systems policy transition from Durable Medical Equipment (DME) to Pharmacy Services benefit.

4. Clinical Presentations

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

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

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

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

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

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

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

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

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

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

5. Public Comment on any DUR Board Requested Report

6. DUR Board Requested Reports

a. Opioid utilization – top prescribers and members

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

b. Top opioid prescribers and top benzodiazepine prescribers

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

7. Public Comment on any Standard DUR Report

8. Standard DUR Reports

a. Review of Prescribing/Program Trends.

1. Top 10 Therapeutic Classes for Q2 2019 and Q3 2019 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR)

1. Review of Q3 2019.
2. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR)

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

9. Closing Discussion

a. Public comments on any subject.

b. Date and location of the next meeting.

1. Discussion of the time of the next meeting.

c. Adjournment.

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

This notice and agenda have been posted at http://dhcfp.nv.gov/and http://notice.nv.gov Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a copy of the meeting materials will be mailed to you. Requests and/or written comments may be sent to the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701, at least three days before the public hearing.

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

Note: We are pleased to make accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at 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.

Summary of the DUR Board

Drug Use Review Board

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

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

The DUR Board meets quarterly to monitor drugs for:

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

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

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

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

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair

Netochi Adeolokun, Pharm.D., Vice Chair

Mark Canty, MD

Jessica Cate, Pharm.D.

Dave England, Pharm D

Mohammad Khan, MD

Brian Le, DO

James Marx, MD

Michael Owens, MD

Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2020

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

Web References

Medicaid Services Manual (MSM) Chapter 1200:

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

Drug Use Review Board Bylaws:

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

Drug Use Review Board Meeting Material:

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

Social Security Act, 1927:

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

Meeting Minutes

DRUG USE REVIEW BOARD

Meeting Minutes

Date of Meeting: Thursday, October 17, 2019 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: Hyatt Place Reno -Tahoe Airport
1790 E Plumb Lane
Reno, NV 89502
Phone: (775) 826-2500

ATTENDEES

Board Members Present
Paul Oesterman, Pharm.D., Chair
Netochi Adeolokun, Pharm.D.
Mark Canty, MD
Dave England, Pharm.D.
Mohammad Khan, MD
James Marx, MD
Jim Tran, Pharm.D.

Board Members Absent
Brian Le, DO
Michael Owens, MD
Jennifer Wheeler, Pharm.D.

DHCFP
Holly Long, Supervising Social Services Program Specialist
Beth Slamowitz, Pharm.D.
Julie Slabaugh, Deputy Attorney General
Tammy Moffitt, Social Services Chief III, Pharmacy Services
Antonio Gudino, Social Services Program Specialist

DXC
KayLynn Wight, RPh

OptumRx
Carl Jeffery, Pharm.D.

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

Public
Jeremy Short, Avexis
Andrea Stratton, Avexis
Melissa Sommers, Novartis
Amy Rodenburg, Allergan
Mari Nakashima
Doug Buriani, Sobi
Robert Jones, GSK

Public Online:
Daniel C Medina
Jan Brooksby, Smith & Nephew
Katie Kucera
Jeana Colabianchi, Sunovion
Chris Stanfield
Cuong Le, OptumRx
Trey Delap
Crystal Riggs

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 1:03 PM.

PO: We have a quorum; we will call the meeting to order.

Roll call

KayLynn Wight, DXC
Tammy Moffitt, DHCFP
Antonio Gudino, DHCFP
Holly Long, DHCFP
Carl Jeffery, OptumRx
Julie Slabaugh, Attorney General's Office
Paul Oesterman, Pharmacist in Reno
Mohammad Kahn, Psychiatrist in Las Vegas
Netochi Adeolokun, Pharmacist in Reno
Jim Marx, Pain and Addiction Physician in Las Vegas
David England, Pharmacist in Las Vegas
Jim Tran, Pharmacist in Las Vegas
Mark Canty, Geriatrician in Reno
Tom Beranek, SilverSummit Health Plan
Ryan Bitton, Health Plan of Nevada
Lisa Todd, Anthem

2. Public Comment on Any Matter on the Agenda

Paul Oesterman, Chair: Do we have any public comment on any topic?

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from July 25, 2019

Paul Oesterman, Chair: Do we have a motion to approve the meeting minutes from the July 25, 2019 meeting?

Motion and second to approve the minutes as submitted.

Voting: Ayes are unanimous, the motion carries.

b. Status Update by DHCFP

Holly Long: I'm Holly Long with DHCFP. In recognition of the International overdose Awareness day, Governor Steve Sisolak proclaimed Saturday August 31 as Overdose Awareness Day for Nevada. Also, I wanted to provide some statistical information regarding the impact of Assembly Bill 474. There was a report that was created by the Board of Pharmacy if all of you will remember. Assembly Bill 474 was from the 2017 Legislative Session, that required specific information on controlled substance prescriptions like patient date of birth, ICD-10 codes, DEA numbers and so-forth. It also required reporting of drug overdoses by healthcare providers and required providers to check the controlled substance history within the PMP or the prescription monitoring program. Requirements from writing an initial prescription such as patient risk assessment and informed consent. Prescriptions written for treating pain for more than 30 days, for more than 90 days and also for exceeding 365 days in a rolling period. Since the implementation of these requirements which were mandated by January 1, 2018, we have been trying to monitor and watch what the effects have been. The Board of Pharmacy put together a good statistical analysis on this. These numbers have been provided in other public forums as well. This is not specific to Medicaid, but Nevada as a whole. In comparing the prescription rates from 2016 to 2018, there has been a 52% decrease statewide in the number of opioid prescription rates. The total number of potential doctor shoppers decreased from 2013 to 2018 by 96%. There was an increase in PMP queries from year to year starting with 2014 to 2018 ranging from 29% to 51%. The opioid prescriptions with less than a 30-day supply decreased by 53%. Opioid prescription with greater than or equal to a 30-day supply but still less than a 90-day supply decreased by 24%. Opioid prescriptions with greater than or equal to 90-day supply decreased by 50%. The number of individuals co-prescribed an opioid and benzo during the same month also decreased significantly which was 54%. By county, all Nevada Counties demonstrated a decrease in both the number and in rate of opiate prescriptions by month ranging from 25% such as Lincoln County up to 56% in Humboldt County. The number of opiate deaths from 2010 to 2018 has started to decrease. I also wanted to provide a DHCFP policy update. The DUR edits that were required from Senate Bill 378 from the recent 2019 Legislative Session were implemented on October 1, 2019. Some edits we already had in place, but any that were not in place have been implemented. I have a list of those edits if anyone needs them.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Zolgensma (onasemnogene abeparvovec-xioi).

Paul Oesterman, Chair: Our first topic is the discussion and possible adoption of prior authorization criteria and/or quantity limits for Zolgensma. Is there any public comment?

Jeremy Short, Region Medical Director with Avexis: Zolgensma is the first and only gene replacement therapy that has been approved to treat spinal muscular atrophy in pediatric under the age of two. It is given as one-time intravenous dose over 60 minutes. It is the only therapy thus far that targets the root cause of SMA which is caused by mutations in the SM1 gene. SMA has an incidence of 1 in 10,000 live births and is characterized by the rapid degradation of the function of the lower motor neurons or spinal motor neurons which leads to progressive muscle weakness. In natural history, Type 1 SMA, we see that over 90% of those patients would not survive to the age of two without intensive therapy. We did have some comments on the proposed prior authorization guidelines. There is language in number two a and b that defined the appropriate patient population. Under 2a, it is talking about the symptomatic patient population and is specifically calls out patients with the diagnosis of SMA type one or two and less than two years of age. This is largely consistent with our label. The only comment we would make is in regards to the specific calling out type one and two patients. There is expert consensus that are covered in the review about treating individuals with three copies of the backup gene SMA 2. You could theoretically have a patient who is an early onset type three patient who has symptom onset between one and half and two years of age and the expert consensus would guide us to say that patient should be treated with three copies. You could potentially miss that patient with how it is worded now. Our suggestion would be to just drop the specific wording of type one and two and leave it more to the label to treat a patient with SMA regardless of time. The second part under two B, it is talking about the pre-symptomatic population. It looks good talking about three copies or less of SMN two. The one thing we would mention is the stipulation is the patient be less than or equal to six months of age who is pre-symptomatic. Naturally you are going to catch these patients pretty early on most of the time if they are being diagnosis with newborn screening. On the off-chance you had a patient that did not present with symptoms until seven months of age, maybe they had three copies of SMA two, expert consensus guides that you would want to treat that patient. We know that the outcomes are betting the earlier treatment is initiated. The best chance of efficacy would be to treat prior to symptom onset. You would not want to force a patient to undergo irreversible motor neuron loss just in order to show symptoms to be a candidate for treatment. I guess we would recommend alter the age limit to be in line and consistent with two A that is talking about less than two years of age rather than six months. One of the common questions we get is durability with this being a new therapy. Our completed phase one study with 15 patients with SMA type one. All of those were on the proposed therapeutic dose and they had the option to enroll in long term follow up study. I am happy to address any questions.

Paul Oesterman, Chair: Our binders have the new format with the Optum recommendations and separate acceptance or additional recommendations from our managed care organizations.

Carl Jeffery: This is a novel gene therapy. It is a one-time dose for the treatment of spinal muscular atrophy. If this is being billed through a physician's office, any PA criteria we add today will not apply. Our proposed criteria mirrors what is on our commercial criteria.

Dave England: How is this diagnosed? In the hospital?

Jeremy Short, Region Medical Director with Avexis: If you have new born screening, which this is not included in Nevada, that would be one way. Family history but usually with symptom onset.

Then they go through the pathway to see a specialist for diagnosis. Unfortunately, when that happens, they suffer irreversible motor neuron damage. With any other currently available disease modifying therapies your best case for halting disease progression is to implement treatment as early as possible. This could be administered in the physician's office. The clinical trials, the patients were kept inpatient, but there is no indication that needs to be done.

Carl Jeffery: The Optum criteria follows to label. We just want to make sure the appropriate people are getting this treatment.

Lisa Todd: I don't have anything to add.

Ryan Bitton: Neither does HPN.

Tom Beranek: I added a couple things, but I am ok with consensus.

Paul Oesterman, Chair: The question is on two A and two B, bullet point one, removing the specificity of type one or two. On B, changing the age from six month to less than two years of age. I would had for a patient not be able to receive treatment because they are six months and one day. The two years makes sense to be consistent. In terms of symptomatic type one or two. If we list those, we might have to come back in a short amount of time to redo the criteria. My proposal would be to accept the prior authorization guidelines with those two changes. The elimination of type one or type two in A one and changing the age limit on B three to two years.

Motion and second to accept revised criteria.

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 narcolepsy agents.

Paul Oesterman, Chair: We have the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for narcolepsy agents. Do we have any public comment?

Carl Jeffery: There is a new medication, Sunosi. It is indicated for the treatment of narcolepsy and sleep disorder related to obstructive sleep apnea. Similar to our current criteria for Provigil and Nuvigil and criteria for Xyrem, we wanted to make sure the class is whole. The criteria is similar. The member has a diagnosis of narcolepsy confirmed by a sleep study, try and failure of Provigil and Nuvigil. For reauthorization, documentation of a positive clinical response. For obstructive sleep apnea, a diagnosis of obstructive sleep apnea defined by 15 or more obstructive respiratory events per hour of sleep confirmed by a sleep study or five or more obstructive respiratory events per hour of sleep confirmed by a sleep study and one of the listed symptoms. Reauthorization criteria is straightforward with documented positive clinical response.

Lisa Todd: I don't have anything to add.

Ryan Bitton: Nothing to add.

Tom Beranek: Do we have an age of 18 or older?

Jim Marx: How do they define obstructive sleep apnea? I'm not sure what an event is.

Carl Jeffery: I'm not familiar with the diagnosis process.

Jim Marx: It would be nice to clean up the language. I think it is too vague.

Paul Oesterman, Chair: How does the rest of the group feel about the 18 years old? I have never seen narcolepsy in pediatrics.

Netochi Adeolokun: The approval length, is that based on the studies?

Carl Jeffery: I'm not sure.

Paul Oesterman, Chair: I think they should both be the same.

Dave England: Does it ever get better? I can see six-month approval to see if things are getting better. Checking for effectiveness or no further progression.

Paul Oesterman, Chair: Are we getting any requests for this currently?

Carl Jeffery: Nothing yet. The utilization numbers are in the binder. Through June, there were not any claims.

Paul Oesterman, Chair: Do we want to table this and bring it back next time with more information on obstructive sleep apnea and narcolepsy? And also clarify the approval length of six or 12 months.

Jim Marx: I think what the effect of that will be is that it will require the patient actually have a sleep study rather than someone saying they saw it happen three times.

Dave England: I would think you would want to do the sleep studies before you prescribe this as opposed to having trouble sleeping.

Carl Jeffery: The criteria does state they have 15 or more obstructive events per hour of sleep confirmed by a sleep study unless the prescriber provides justification confirming a sleep study would not be feasible. That is listed in one A and one B.

Paul Oesterman, Chair: This will be tabled to the next meeting.

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

Paul Oesterman, Chair: Our next topic is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for hematopoietic/hematinic agents. Do we have any public comment?

Carl Jeffery: We are going through our old criteria that has not been reviewed for a long time and bringing it to the board for review. The binder has Chapter 1200 criteria. On page 61, I did suggest one minor change that the recipient has been evaluated for adequate iron stores. The rest of the criteria is the same.

Paul Oesterman, Chair: One question I have, many patients are end-stage renal disease, which is covered by Medicare?

Carl Jeffery: This is included in the Medicare daily rate, so there should not be any dialysis patients receiving this through Fee-for-service. The utilization shows on page 62, there is a spike related to one pharmacy that is misidentified in the system and that will be corrected.

Paul Oesterman, Chair: Has the P&T reviewed this?

Carl Jeffery: Yes, we just reviewed this at the last meeting.

Paul Oesterman, Chair: The only amendment is the evaluation of iron stores?

Jim Marx: All these agents increase fibrinogen which increase the incidence of DVT. I wonder if we should have an educational component in the criteria?

Carl Jeffery: That is a black-box warning. We always walk the line of what is the responsibility of the DUR Board. This is enforced by the FDA. The call center suggested, under two B, if it is for pre-operative use, should that be included. And they asked if the exclusion could be cleaned up to make it more clear. But I think that is something we could clean up later.

Holly Long: Is it necessary to have the non-covered indications?

Carl Jeffery: I think it is good to have that. Some are medically indicated, but they are covered through other means.

Paul Oesterman, Chair: What do the managed care organizations have to say?

Lisa Todd: I don't have anything to add.

Ryan Bitton: I think the criteria works. We use hematocrit instead of hemoglobin, but I don't think that makes a big difference. Our criteria doesn't call out other indications like hepatitis C and non-dysplastic disease. For anemia due to chemotherapy, there is a two-month limit.

Jim Tran: One thing the guideline goes up to 11, which can increase cardiovascular death. I wonder if we could adjust the range.

Paul Oesterman, Chair: I know a lot of places with the protocols, it is given once per week. If the hemoglobin increases greater than one gram, they do a 25% reduction in the dose the following week. I don't know how that would be incorporated or if this will be a standard dose.

Carl Jeffery: We don't PA the specific dose, we don't get down to that level.

Paul Oesterman, Chair: Jim, would you make the recommendation then under criteria number two to maintain hemoglobin levels up to 11?

Jim Tran: Yes, up to 11.

Paul Oesterman, Chair: Any other recommendations to modifications? We will call for a motion to approve the criteria as presented with an update for the inclusion of adequate iron stores and modifying the hemoglobin levels to up to 11 grams per deciliter.

Motion and second to accept amended proposed criteria.

Voting: Ayes are unanimous, the motion carries.

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

Paul Oesterman, Chair: Our next topic is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Regranex. Do we have public comment?

Carl Jeffery: This is another criteria where we wanted the board to review. On page 82, I have one recommended change that includes treatment in combination with ulcer would care to prevent infection.

Paul Oesterman, Chair: Do the MCO's have any input?

Lisa Todd: We talk about the diagnosis, we have a note included that the ulcer is stage three or four in the international association for interstomal therapy guide to chronic staging. That was the only difference.

Ryan Bitton: Nothing from HPN.

Tom Beranek: The only thing that we had suggested adding was a dose limit of one tube.

Paul Oesterman, Chair: I think it is possible to incorporate that. I agree the limitation should be foe stage three and four chronic sores.

Jim Marx: What about large ulcers, is one tube enough?

Tom Beranek: In the majority of cases, you only need one tube. In the rare case you need more, you could get an override.

Paul Oesterman, Chair: This one is five-month approval, different than others.

Lisa Todd: I think that is due to the length of therapy.

Carl Jeffery: This is part of wound care, if they are not getting better after five months, they need to reassess therapy.

Jim Tran: The guidelines state after 20 weeks if no healing, the treatment should be reassessed.

Carl Jeffery: From a Fee-for-service side, we don't see very much utilization. Some months don't see any claims, some months three claims. We may consider if we need criteria at all.

Paul Oesterman, Chair: Let's take away the prior authorization and add a quantity limit. The quantity limit of 1 tube.

Carl Jeffery: If we just have a quantity limit, we don't need to have it in Chapter 1200. Then it doesn't need to be maintained by the DUR Board.

Motion to remove the prior authorization criteria. Second.

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 topical, local anesthetics.

Paul Oesterman, Chair: The next topic is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical, local anesthetics. Do we have any public comment?

Carl Jeffery: This is one more we are bringing to the board. There are several new products like ZTLido. They add another product to make them a little different.

Jim Marx: I can tell you the ZTLido works much better than the Lidoderm. Patients find them much more effective.

Carl Jeffery: These are only indicated for postherpetic neuralgia.

Jim Marx: It is effective for many other conditions. I don't think there is adequate literature to support, like muscular-skeletal pain.

Carl Jeffery: Right now, the criteria is limited to Lidocaine patch specifically. I think we want to include other products. Utilization is on page 93, we do have a significant amount of claims. Lidocaine patches are non-preferred, but we still see a lot of use.

Paul Oesterman, Chair: I know there are some products available now over the counter with these ingredients. Should these all be incorporated into this class rather than one for 5% patches?

Holly Long: The over the counter is a little different since they require a prior authorization.

Carl Jeffery: I don't know what they are indicated for off the top of my head. The just need a prescription for coverage.

Paul Oesterman, Chair: What do the MCO's have to say?

Tom Beranek: I am good with the recommendation from Optum.

Ryan Bitton: The criteria that Optum has for post-herpetic neuralgia, does that include neuropathy? In our plan we cover for neuropathy after they try a tricyclic, SNRI or gabapentin. We have a path for the Lidocaine patches for neuropathy.

Lisa Todd: Ours is just for post-herpetic neuralgia.

Paul Oesterman, Chair: We have a difference from what the MCO's have compared to Fee-for-service.

Jim Marx: In this era of opioid sparing, we have these non-opioid treatments available that can be effective, I would like to see these more open like where HPN criteria with a neuropathy indication. It would make sense to me to open these up.

Dave England: I agree, we have the same issue with getting people to reduce their opioid, we try to get people on these patches in place of an oral opioid. They seem effective and happy with them.

Paul Oesterman, Chair: I found the same in the hospital patients.

Beth Slamowitz: Does the indication include neuropathy or just post-herpetic neuralgia?

Carl Jeffery: As far as I know, it is just post-herpetic neuralgia.

Beth Slamowitz: We are restricted to cover it only for FDA-approved indication, which is post-herpetic neuralgia.

Paul Oesterman, Chair: I think we are limited to what we can do with the prior authorization guidelines to post-herpetic neuralgia. I can see two options, we can approve the criteria as presented or we can remove the prior authorization requirements. Do the managed care organization feel they need to keep the criteria?

Ryan Bitton: We recommend keeping the criteria.

Lisa Todd: We are the same.

Paul Oesterman, Chair: I don't think there are any changes presented here, do we have a motion to approve the criteria as presented?

Motion and second to approve the criteria as presented.

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 inhaled anticholinergic agents.

Paul Oesterman, Chair: Our next item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for inhaled anticholinergics. Do we have any public comment?

Carl Jeffery: One more old criteria. The criteria is only one anticholinergic product be used within a 30 day period. We have some long-acting anticholinergic and I could see using these in combination with a short-acting product for rescue. I think the criteria is outdated.

Paul Oesterman, Chair: I'm questioning if we even need prior authorization criteria.

Carl Jeffery: Page 109 has the utilization. The Advair Diskus decreased with the introduction of some generics.

Paul Oesterman, Chair: Do we have data showing that there are patients using multiple anticholinergic agents at the same time?

Carl Jeffery: We shouldn't see that because the PA criteria does not allow multiple products.

Ryan Bitton: We are ok with removing criteria. We have the class on the preferred drug list.

Lisa Todd: We are like HPN. We have a quantity limit set.

Tom Beranek: I don't have anything to add.

Paul Oesterman, Chair: These are such widely used medication. Do we need prior authorization? We could manage with a quantity limit? Do we have a motion to remove the prior authorization criteria and just have a quantity limit of one unit for 30-day limit?

Motion and second to accept the removal of the prior authorization criteria and add a quantity limit of one unit per 30 days.

Carl Jeffery: I just want to clarify; the intent is to allow one long-acting unit and one short-acting unit. I just want to make it clear for the minutes. One of either long-acting or one short-acting agent.

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 Daliresp (roflumilast)

Paul Oesterman, Chair: The next topic is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Daliresp. Do we have any public comment?

Carl Jeffery: This is old criteria. Our utilization on page 135, about 20 to 25 claims per month. We wanted to evaluate the criteria to make sure it is still necessary. I don't have any recommended changes. Under D, to remove the severe part so it would just read COPD.

Lisa Todd: The only thing is that we have some items that it would not be approved for. A diagnosis of moderate Child-Pugh B or severe Child-Pugh C hepatic impairment. Also individuals using with concomitant CYP-450 enzyme inducer. Or requesting to treat acute bronchospasm.

Paul Oesterman, Chair: Would the drug interactions be picked up by the filling pharmacy?

Carl Jeffery: I don't think we have any hard-stops for drug-drug interactions. It would be a soft-stop for the pharmacist to evaluate the interaction.

Ryan Bitton: We are ok with the criteria with the addition of very severe COPD.

Tom Beranek: Our criteria requires it be prescribed with a long-acting bronchodilator and the dose is limited to 500 mcg per day or one tablet.

Paul Oesterman, Chair: When will the generic be available?

Carl Jeffery: This is not on my radar, I'm not sure.

Holly Long: Is there a reason to removed Severe?

Carl Jeffery: That was the recommendation from the call center and also remove the term chronic bronchitis of COPD. I think it is because the way the diagnosis is made.

Dave England: There has been a generic approved, but it is not on the market yet.

Carl Jeffery: They recommend removing the severe language because we require failure of three other medications implies the condition is severe. And also remove the chronic bronchitis term because it can be used without chronic bronchitis.

Mark Canty: There is no diagnosis for severe vs mild or moderate, so how would we know? It should be for severe, but it is subjective to the provider.

Paul Oesterman, Chair: Do we have any information on if patients stay on this for a long time?

Carl Jeffery: I have not looked at the durability. The utilization shows 44 members and it is consistent through the year.

Paul Oesterman, Chair: We have the guidelines with recommendation to remove "Severe" from D and remove "Chronic Bronchitis" from D also. Does anyone feel the need to include the exclusion criteria that Lisa was talking about? Child-Pugh hepatic impairment and CYP-450 inducers. The indication does say it is not indicated for acute treatment.

Mark Canty: What about the concomitant use with another bronchodilator. I can't imagine someone is not going to be on another treatment.

Paul Oesterman, Chair: We have the proposed criteria with removing "Severe" and "Chronic Bronchitis", the question to the board is do we want to add the Child-Pugh hepatic impairment or not.

Dave England: I move to include it.

Second.

Paul Oesterman, Chair: The motion is to approve the prior authorization guidelines with everything as is, removing the "Severe" and "Chronic Bronchitis" language from D and then include a contraindication of individuals with a diagnosis of moderate Child-Pugh B or severe Child-Pugh C hepatic impairment.

Motion and second to accept the criteria as amended.

Voting: Ayes are unanimous, the motion carries.

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

Paul Oesterman, Chair: The next item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical antiparasitics. Do we have any public comment?

Carl Jeffery: This starts on page 145. We are proposing the removal of Natroba criteria because we are singling out this agent and there is also a limited supply of Sklice. It would be easier to remove the criteria. Sklice should be available at the end of 2020.

Paul Oesterman, Chair: Do any of the managed care organizations have a problem with removing the criteria?

Ryan Bitton: No.

Paul Oesterman, Chair: Do we have a motion to remove the prior authorization criteria?

Motion and second to remove the prior authorization criteria.

Voting: Ayes are unanimous, the motion carries.

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

Paul Oesterman, Chair: Our next topic is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical immunomodulators. Do we have any public comment?

Carl Jeffery: The P&T asked for this review. There is a letter of support for Eucrisa. You can see in the utilization the drop for when the Board added criteria. I don't have any recommended changes.

Holly Long: The letter is printed and is in front of everyone and is at the table by the door. We had about 11 or 12 providers supporting Eucrisa to be preferred.

Netochi Adeolokun: I have heard good things about Eucrisa. I think we should take away the requirement for a trial of a steroid for two weeks before getting it.

Carl Jeffery: If we do that for Eucrisa, we lump them in with Protopic and Elidel as well, do we pull out Eucrisa?

Paul Oesterman, Chair: What do the MCO's have to say?

Tom Beranek: We are in line with Fee-for-service. We have a different age of 16 vs. 18 for Protopic.

Ryan Bitton: We are also in line with the current recommendations.

Lisa Todd: Us too with Anthem.

Jim Marx: Are we still going to require a failure of a topical steroid? The problem with that is this creates complications before even starting.

Paul Oesterman, Chair: Do we have a recommendation to remove?

Jim Marx: I think this should be used first-line.

Dave England: The other agents do have some black-box warning, we are requiring something more toxic?

Paul Oesterman, Chair: Under coverage and limitations, "A" and "E" is similar except "E" specifies Eucrisa.

Dave England: How do we tweak the verbiage to allow it to be used first?

Paul Oesterman, Chair: It doesn't seem there is a sequential order, any of the topical agents could be used. Do we want to change the age for Protopic to 16?

Mark Canty: The topical steroids are so full of problems.

BS: The FDA website says Protopic 0.1% can be used in adults 16 years of age and older, the 0.03% can be used in children two to 15 years.

Paul Oesterman, Chair: We have revised the guidelines to three changes. One, removal of bullet point A, second eliminating bullet point E and changing the age of Protopic to age 16 and older.

Motion and second to approve the updated guidelines.

Voting: Ayes are unanimous, the motion carries.

j. **For Possible Action:** Presentation, discussion and possible adoption of updated DUR Bylaws

Paul Oesterman, Chair: That completed the clinical presentation. We have one more topic here, the presentation, discussion and possible adoption of updated DUR Bylaws. Is there any public comment?

Holly Long: We are bringing this back again. We had some suggestions made by Julie that we remove the public comment piece. We made a lot of updates last time. The only we are doing now is removing the public comment piece that starts on page 11 and goes to page 12. That was not in alignment with open meeting laws. I do need everyone to vote and it has been approved by the director.

Paul Oesterman, Chair: It seems straightforward, we just have the changes to remove the public comment section to be in compliance with open meeting laws. Any discussion?

Motion and second to approve the updated bylaws.

Voting: Ayes are unanimous, the motion carries.

5. DUR Board Requested Reports

Paul Oesterman, Chair: We have our Board requested reports. Our first is the opioid utilization.

Carl Jeffery: Page 171 is where this starts. We added the morphine equivalent dose. The top prescribers changed now, so the top prescribers are listed. We have an anesthesiologist in the top that is quite a bit higher than the others. The members are on the next page.

Jim Marx: The sum of the MED is the entire dose?

Carl Jeffery: I multiples the total number of units by the conversion factor to get the final column.

Dave England: Is the anesthesiologist a surgery center?

Carl Jeffery: No, these are only Fee-for-service claims. These specialties are all self-reported.

Paul Oesterman, Chair: When was the last time we lettered the prescribers?

Holly Long: January.

Jim Marx: The first three prescribers, their MME per day is 59 then 74 and 78, so these are not huge numbers. The MED's per day are not much of a concern. Some are as low as 20.

Paul Oesterman, Chair: It would be interesting to see at the next meeting to see the impact of the letter that went out in January. And maybe send another letter as an FYI to let them know where they stand.

Carl Jeffery: The overall utilization is trending down.

Jim Marx: These MME's are very reasonable. My MME's are a lot higher, but if I got a letter, I would get a little miffed.

Holly Long: The letter is informative not threatening. It goes through the DAG. It lets them know the Board reviewed the information and they are identified as one of the top prescribers.

Jim Marx: I think you may be creating the wrong impression among prescribers. You may create a bad rapport with these letters. I think some prescribers are already paranoid and some prescribers have stopped prescribing opioids. I think this is the wrong approach.

Mark Canty: What would you recommend, what MME would you be concerned.

Jim Marx: My MME is probably 250 per day, but I'm in pain management and every practice is different.

Holly Long: Education is a big piece, so if you have recommendations for education, we can pursue that.

Jim Marx: Prescribers need to know how to taper and how to arrive at the appropriate dose.

Dave England: I was looking for CE on how to deal with opiate prescribing, I can't find anything out there. What other criteria or options do we have? We used to have some education programs with the College of Medicine. We can't just tell them what not to do, but we need to give them alternatives. I agree with Dr. Marx, we may be barking up the wrong tree. Can we put together a program or webinar?

Holly Long: I think that is a great idea. If you have ideas, we can put that on the Division's website. The statistics I presented earlier show the polices are effective. Now what more can we do? What can Medicaid realistically cover like massage or chiropractors that would help?

Dave England: Since we push decreased opioids, are we seeing any trends where we see an upswing? Are we doing a better job with alternatives or are they going somewhere else for their pain treatment.

Holly Long: We can try looking at chiropractor requests or are people seeking acupuncture. I don't have access to that data.

Carl Jeffery: You will see in the overall utilization, gabapentin has moved up, so there is a shift in prescribing.

Paul Oesterman, Chair: In the hospital setting, I am seeing a lot more intravenous acetaminophen. Patients are doing just fine.

Holly Long: We can look at other claim information for this, but if we want to look at something bigger, we can entertain those ideas. I am always looking at other states, and many can't claim the same success we have.

Mark Canty: Have you seen methocarbamol increasing? Using that rather than opioids.

Paul Oesterman, Chair: The restrictions on carisopradol many hospitalists are moving toward methocarbamol or Flexoril.

Mark Canty: Seems like a pain indication though.

Jim Marx: I think it is a safer alternative than some others. Even gabapentin is falling out of favor.

Carl Jeffery: It hasn't popped up, but it might be good to look at muscle relaxants. Maybe that is where patients are going.

Dave England: The pain needs to be treated somewhere. I don't think we see the whole picture.

Jim Marx: Quality of life and productivity has gone down as well. There are other factors are not measuring.

Holly Long: There are many instances where friends and family see addiction in a short amount of time.

Paul Oesterman, Chair: I think we have discussed this quite a bit. If anyone has other ideas, send them to Holly.

Carl Jeffery: I do have a couple more details, the report is by member with the MME. I pulled the detail for the top members so you can see what they are getting. These are just opioids.

Jim Marx: Remember we looked at acetaminophen a few years ago. Have we looked at that again?

Carl Jeffery: Looking at the top ten, there are just a few members getting the combo products with acetaminophen. The methadone is not calculated in here because of the variability of the dose. Page 175 we move to the benzos. The first page shows the top ten prescribers. These quantities don't really alarm me.

Paul Oesterman, Chair: We were looking for the combination of the opioid and benzo.

Carl Jeffery: Right, that is what we are seeing here. These are the top ten prescriber who are also prescribing opioids for those members. So, these members are also on an opioid.

Paul Oesterman, Chair: Can we get a report that shows by patient that is on the benzo and opiate. To see if there is anyone getting excessive amounts.

Carl Jeffery: It's hard to present that while maintaining PHI, but I will try getting something like that.

Paul Oesterman, Chair: Do any of the managed care organizations want to highlight some outliers?

Ryan Bitton: We see the same trend, nothing really we need to call out.

Lisa Todd: We looked at the top opioid prescribers, they were no the top benzo prescribers, we did not have any overlap.

Tom Beranek: We see the same for SilverSummit. The opioid and benzos, two doctors stand out, so we are sending them letters. We haven't received a response yet. The top members are on the list because they are using Suboxone products.

Carl Jeffery: On page 176 is the Fee-for-service report you are looking for. This shows the opiate prescribers and the letter match back to the top ten opioid from the opioid report. Then it goes over to what benzo they were prescribing and how many. So, this shows our top opioid prescribers are not big benzo prescribers.

Ryan Bitton: We had 12,000 members using an opioid, 4,000 using a benzo and 1,500 on a combo. Most patients using opioids are not using benzos.

Lisa Todd: I did run the top benzo prescribers for first quarter and second quarter. There were five benzo prescribers that showed up in each quarter in the top. Otherwise, none of the prescribers are in the top ten opioid prescribers.

Paul Oesterman, Chair: Sounds like our prescribers are doing good things.

Tom Beranek: I looked at our top opioid utilizing members, of the top ten, four are seeing a physician that also shows as the top prescribers. We are sending them letters.

Mark Canty: Are members on hospice in the Fee-for-service program?

Carl Jeffery: We can look, but hospice will be paying for most opioids and benzos, so we don't get that information.

Paul Oesterman, Chair: The next report is the lock-in program.

Carl Jeffery: Page 178, we have 886 patients in lock-in, we have added three, two and six members in the past three months. We send a list of members to DHCFP every month with twelve or more controlled substances within 60 days, two or more prescribers and two or more pharmacies. We send that list to DHCFP and review the diagnosis and let us know who to lock-in. The numbers we lock-in are moving down every month.

Holly Long: This information that goes to a nurse at DHCFP who also reviews the PMP report.

Paul Oesterman, Chair: Have we been able to reduce the members in lock-in?

Holly Long: We don't ever remove someone from lock-in. Once they are locked-in, they don't have a chance to abuse and go other places. After we made the form to change pharmacies, we have received fewer complaints.

Tom Beranek: We are trending the same, about 60 or 65 members. We dropped down to 58 because if they don't have a claim for a year, we drop them from lock-in.

Ryan Bitton: We have 444 and added 24 in the second quarter. We review every year and most stay locked-in.

Lisa Todd: For Anthem, we started with 373. We are looking at more than pharmacies claims like behavioral health to see if there is an opportunity to see if they may benefit from case management. Maybe they need help elsewhere.

Jim Marx: What is the procedure with a supply chain problem. If a pharmacy can't get a certain medication?

Holly Long: That would be a call on a case-by-case bases and they would be given an override.

Paul Oesterman, Chair: Next we have naloxone prescriptions for members receiving opioids.

Carl Jeffery: I put a summary on the top of the page of how many received a prescription for the naloxone nasal spray. We have 303 members on opioid with a naloxone prescription and it goes down from there, 280 with two prescriptions of Narcan. I broke down to what opioids people are getting that are receiving the nasal spray. The highest number with the hydrocodone and acetaminophen products.

Jim Marx: Why would someone get naloxone and Suboxone at the same time?

Carl Jeffery: They may not be overlapping, this is a year's worth of data. So maybe they started treatment.

Paul Oesterman, Chair: MCO's, similar numbers?

Ryan Bitton: We had about 28,000 opioid claims and 224 naloxone claims, so about 0.8%. Of the 28,000 claims, there is a small amount of naloxone. First quarter we saw an increase in claims but tapered off.

Paul Oesterman, Chair: I think there could be an education opportunity for prescribers that naloxone is available.

Tom Beranek: Looking at the total opioids is going down and naloxone is going up, a good trend.

Paul Oesterman, Chair: I wonder how many are getting refills on the naloxone?

Dave England: Could we look at hospital admissions?

Carl Jeffery: That is hard data to get. If they are admitted for something unrelated, they may have opioid abuse diagnosis.

Lisa Todd: From Anthem, I pulled the data from January to June, we had 539 member that received naloxone.

Jim Marx: Is there a way to break down chronic use vs. acute use. The chronic users are more likely to have an overdose and I think it is better to focus on getting them appropriate therapy.

Carl Jeffery: We didn't look at chronic vs. acute therapy. I could see if someone getting an acute treatment with an opioid, but they have a high-risk family member, they are a good candidate for getting naloxone.

Paul Oesterman, Chair: Moving to our next report on darbepoetin.

Carl Jeffery: I think we wanted to look at ESRD claims. I pulled a diagnosis where I could, anemia is on the top. Utilization over all is descending for Aranesp.

Tom Beranek: Nothing really to call out.

Ryan Bitton: We looked at place of service, mostly used for cancer.

Lisa Todd: Anthem is the same.

Paul Oesterman, Chair: Our last report is in regards to antimicrobial therapy, third generation cephalosporins, fluoroquinolones and oxazolidinones.

Carl Jeffery: On page 185 to follow along. We did a lot of prep work for this policy, it is starting to creep back up. We have not heard many problems.

Holly Long: Once we explained the policy, I think everything is moving smoothly. I have not received any appeals or phone calls demanding the policy needs a change.

Paul Oesterman, Chair: I think we should send some communication to the prescribers with the antimicrobial stewardship program so they know we look at other things other than opioids.

Carl Jeffery: The proof will be in the isolets if we can show resistance is not as much as it used to be.

Holly Long: Other states are excited to hear how our program is working out.

Tom Beranek: We already had all the drugs on prior authorization, the only one we don't have criteria is the generic ciprofloxacin, it can be used. Our numbers were about the same.

Ryan Bitton: We did see a drop in cefdinir in March and continues to drop. But some of the products where already on the PDL.

Paul Oesterman, Chair: As we get to cough and cold, flu season is we need to let prescribers know it is ok to send a member out without a prescription for an antibiotic.

Lisa Todd: Anthem didn't adopt the criteria, but we do have some of these products on our PDL, we didn't really see the drop-in use like Fee-for-service.

Paul Oesterman, Chair: We received a letter from pulmonary associates requesting smoking cessation added to a future meeting.

6. Standard DUR Reports

Paul Oesterman, Chair: Our standard DUR reports.

Carl Jeffery: Page 187 we have our top ten therapeutic classes. Hemophilia is still number one followed by antiretrovirals and anticonvulsants a little further down. When we look at the report by claim count, we see an increase in gabapentin. The opioids are now dropped to number four.

We still have the beta-agonists toward the top too. We put some quantity limits on albuterol, but they are were not effective at the time of the report.

Paul Oesterman, Chair: Do we still see a decrease in the hepatitis C agents?

Carl Jeffery: Yes, they are dropping significantly. It has not gone away completely. The ProDUR reports are the standard report we see every meeting with drug-drug interactions are the top. Not all of them have hard stops, some are just messages so they will be paid without rejecting. On page 190 shows the specifics for the different messages. The duplicate Rx may be due to our physician administered drug claim processing. Our RetroDUR activities include April letters for diabetics without a statin. In May we reviewed zolpidem utilization, mostly among FDA recommendations for dose in women and long-term use. We also reviewed benzodiazepine use in members over 65 years of age. We also reviewed extended opioid use disorder without cancer or HIV medications who are receiving an opioid.

Paul Oesterman, Chair: Do any of our MCO's have comments?

Lisa Todd: From Anthem, the top ten drug classes. Our antiretrovirals are number one. It is interesting the anticonvulsants by claim count, our NSAIDs went to the top and then we have anticonvulsants are number three. Opioid combos are number nine on the list. Regarding our quarter DUR report, our biggest DUR is therapeutic duplication, early refill and high dose are the top three. Nothing out of ordinary. For RetroDUR, one thing you asked about before, I brought results. The last meeting we reported on medication adherence was one of our clinical programs. They were non-adherent to diabetes medications or cholesterol. We don't ask for letters to be returned from providers, but we take about six months and look at claims to see if there is a positive outcome. We saw a positive outcome, 922 out of 2673 which is 34% positive outcome on that one. A new one we started, called gaps of care. We look at adherence to asthma, cardiovascular guidelines, post MI, statins, a big area of gaps of care. We identified 113 members and there was a positive outcome of 15%. I have two more listed around behavioral health. We have a good positive outcome on that, 299 members identified that were experiencing polypharmacy for behavioral health and we had a positive outcome of 75.9%. We also did an age appropriateness for behavioral health, we had 21 out of 31 member which is 67.7%.

Ryan Bitton: The top ten, opioids and SSRIs swap from quarter one to quarter two. Everything else is the same from cost and claim count. From the RetroDUR, we looked at lots of gaps if care. The one of things we did was look at duplicate HIV regimens. We notify prescribers that the member may be on unnecessary therapy.

Tom Beranek: My comments could almost mirror Lisa's in terms of the top ten drugs from the cost and claim standpoint. The difference with the DUR is the third from the top is ingredient duplication. We continue to choose a new topic for RetroDUR every quarter and send out letters each month.

7. Closing Discussion

Paul Oesterman, Chair: Great. Is there any public comment? The next meeting is here, January 23, 2020.

Holly Long: I would like to announce a big thank you for Dr. Oesterman. Today is his last meeting with us. He has decided to move on. I wanted to thank you for all your years of service and acting as chair for so long. You have been amazing and we appreciate you.

Paul Oesterman, Chair: Thank you. It has been a good experience. The meeting is adjourned.

Meeting adjourned at 3:37 PM.

Clinical Presentations

Prior Authorization Guideline

Guideline Name Multiple Sclerosis (MS) Agents

1 . Indications

Drug Name: Aubagio (teriflunomide)
Relapsing forms of multiple sclerosis (MS) Indicated for the treatment of patients with relapsing forms of MS.
Drug Name: Avonex (interferon beta-1a)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.
Drug Name: Betaseron (interferon beta-1b)
Relapsing forms of MS Indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.
Drug Name: Copaxone (glatiramer acetate), Glatopa (glatiramer acetate)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS.
Drug Name: Extavia (interferon beta-1b)
Relapsing forms of MS Indicated for the treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS.

Drug Name: Gilenya (fingolimod)
Relapsing forms of MS Indicated for the treatment of relapsing forms of MS in patients 10 years of age and older.
Drug Name: Lemtrada (alemtuzumab)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS. Becuase of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Drug Name: Mavenclad (cladribine)
Relapsing forms of MS Indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Limitations of use: Mavenclad is not recommended for use in patients with CIS because of its safety profile.
Drug Name: Mayzent (siponimod)
Relapsing forms of MS Indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
Drug Name: Ocrevus (ocrelizumab)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS. **Primary Progressive Forms of Multiple Sclerosis (PPMS)** Indicated for the treatment of patients with primary progressive forms of MS.
Drug Name: Plegridy (peginterferon beta-1a)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS.
Drug Name: Rebif (interferon beta-1a)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
Drug Name: Tecfidera (dimethyl fumarate)
Relapsing forms of MS Indicated for the treatment of patients with relapsing forms of MS.
Drug Name: Zinbryta (daclizumab)

Relapsing forms of MS Indicated for the treatment of adult patients with relapsing forms of MS. Because of its safety profile, the use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

2 . Criteria

Product Name: Aubagio, Avonex, Betaseron, Brand Copaxone, Generic glatiramer acetate, Glatopa, Gilenya, or Tecfidera, Extavia, Mayzent, Plegridy, Rebif	
Approval Length	12 Month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses) [A-D]

Product Name: Lemtrada	
Approval Length	12 Month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses) [A]

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 Patient has not been previously treated with alemtuzumab

AND

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

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Mavenclad (cladribine)
- Mayzent (siponimod)
- Ocrevus (ocrelizumab)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)
- Zinbryta (daclizumab)

OR

2.2 Both of the following: [E]

2.2.1 Patient has previously received treatment with alemtuzumab

AND

2.2.2 At least 12 months have or will have elapsed since the most recent treatment course with alemtuzumab

AND

3 - Not used in combination with another disease-modifying therapy for MS

Product Name: Mavenclad	
Approval Length	1 Month(s)
Guideline Type	Prior Authorization

Approval Criteria

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

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 Patient has not been previously treated with cladribine

AND

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

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Lemtrada (alemtuzumab)
- Mayzent (siponimod)
- Ocrevus (ocrelizumab)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)
- Zinbryta (daclizumab)

OR

2.2 Both of the following:

2.2.1 Patient has previously received treatment with cladribine

AND

2.2.2 Patient has not already received the FDA-recommended lifetime limit of 2 treatment courses (or 4 treatment cycles total) of cladribine

AND

3 - Not used in combination with another disease-modifying therapy for MS

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

Approval Criteria

1 - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses) [A]

AND

2 - Trial and failure, contraindication, or intolerance to at least two of the following disease-modifying therapies for MS:

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)

AND

3 - Not used in combination with another disease-modifying therapy for MS

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

Approval Criteria

1 - Documentation of positive clinical response to Zinbryta therapy

AND

2 - Not used in combination with another disease-modifying therapy for MS

Product Name: Ocrevus	
Diagnosis	Relapsing Forms of MS
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization

Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses) [A]

AND

2 - Not used in combination with another disease-modifying therapy for MS

AND

3 - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]) [16]

AND

4 - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

Product Name: Ocrevus	
Diagnosis	Relapsing Forms of MS
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Ocrevus therapy

AND

2 - Not used in combination with another disease-modifying therapy for MS

AND

3 - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]) [16]

AND

4 - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

Product Name: Ocrevus	
Diagnosis	Primary Progressive Forms of MS
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a primary progressive form of multiple sclerosis (PPMS)

AND

2 - Not used in combination with another disease-modifying therapy for MS

AND

3 - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]) [16]

AND

4 - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

Product Name: Ocrevus	
Diagnosis	Primary Progressive Forms of MS
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to Ocrevus therapy

AND

2 - Not used in combination with another disease-modifying therapy for MS

AND

3 - Not used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]) [16]

AND

4 - Not used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

3 . Endnotes

A. According to the National MS Society, of the four disease courses that have been identified in MS, relapsing-remitting MS (RRMS) is characterized primarily by relapses, and secondary-progressive MS (SPMS) has both relapsing and progressive characteristics. These two constitute “relapsing forms of MS” if they describe a disease course that is characterized by the occurrence of relapses. [7] The effectiveness of interferon beta in SPMS patients without relapses is uncertain. [6]
B. Initiation of treatment with an interferon beta medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS. [6]
C. Based on several years of experience with glatiramer acetate and interferon beta 1a and 1b, it is the consensus of researchers and clinicians with expertise in MS that these agents are likely to reduce future disease activity and improve quality of life for many individuals with relapsing forms of MS, including those with secondary progressive disease who continue to have relapses. For those who are appropriate candidates for one of these drugs, treatment must be sustained for years. Cessation of treatment may result in a resumption of pre-treatment disease activity. [6]
D. MS specialists will use Copaxone in relapsing forms of disease, including SPMS with relapses. While there have been no trials of Copaxone in SPMS (so we have no evidenced-based data upon which to make decisions or recommendations), it's clear that where there are relapses, the injectable therapies are partially effective – they reduce relapses and new lesions on MRI. In SPMS, the trials suggest that the interferons work better in earlier, more inflammatory (i.e. those with relapses prior to the trial and with gadolinium-enhancing lesions, which is the MRI equivalent of active inflammation). Since Copaxone and the interferons appear to have rather similar efficacy in the head-to-head trials, most assume that Copaxone has a similar efficacy in SPMS: where there are relapses or active inflammation on MRI, it will likely have some benefit. Thus, most MS specialists will use Copaxone in patients with SPMS who have persistent relapses. [8]
E. According to Prescribing Information, the recommended dosage of Lemtrada is 12 mg/day administered by intravenous infusion for 2 treatment courses (first treatment course: 12 mg/day on 5 consecutive days; second treatment course: 12 mg/day on 3

consecutive days administered 12 months after the first treatment course). Following the second treatment course, subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be administered, as needed, at least 12 months after the last dose of any prior treatment courses. [13]

F. Not to exceed the FDA-recommended dosage of 2 treatment courses (with the second course administered 43 weeks following the last dose of the first course). According to Prescribing Information, the recommended cumulative dosage of Mavenclad is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course). Each treatment course is divided into 2 treatment cycles with the second cycle of each course administered 23 to 27 days after the last dose of the first cycle. Following the administration of 2 treatment courses, do not administer additional Mavenclad treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. The safety and efficacy of reinitiating Mavenclad more than 2 years after completing 2 treatment courses has not been studied. [19]

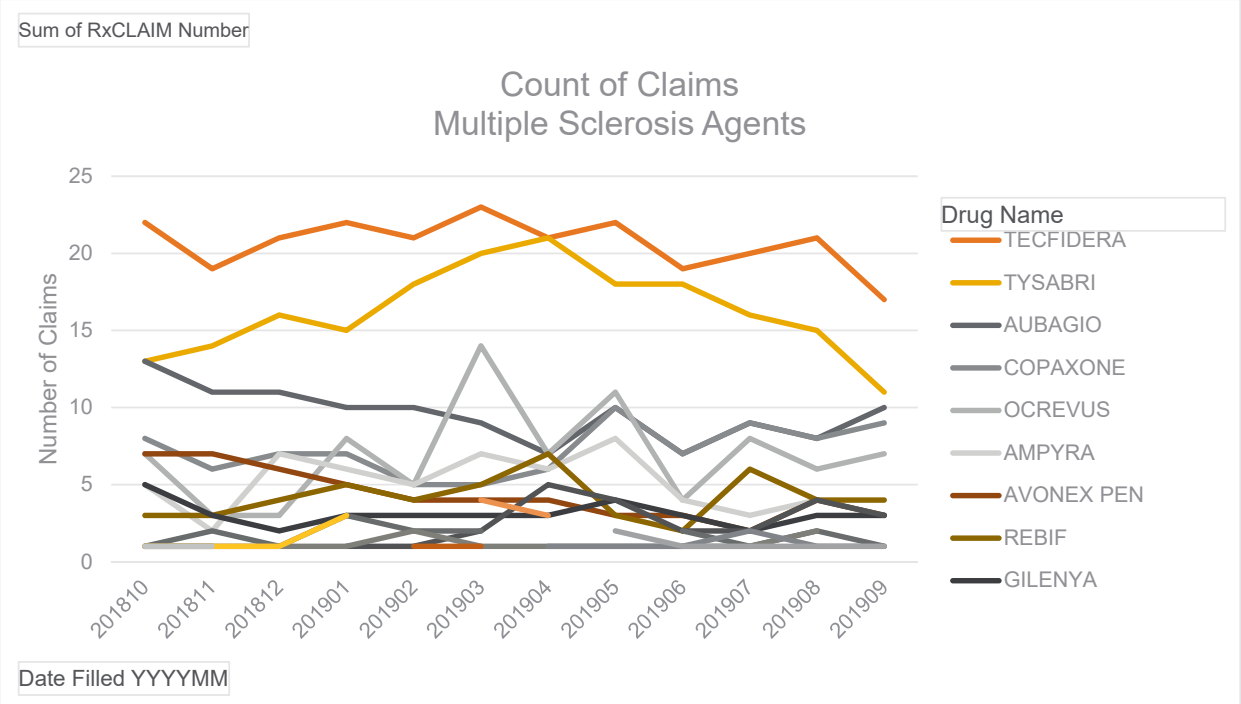
4 . References

1. Avonex Prescribing Information. Biogen Idec Inc. Cambridge, MA. December 2018.
2. Betaseron Prescribing Information. Bayer. Whippany, NJ. August 2018.
3. Copaxone Prescribing Information. Teva Pharmaceuticals. North Wales, PA. October 2018.
4. Extavia Prescribing Information. Novartis. East Hanover, NJ. December 2018.
5. Rebif Prescribing Information. Serono Inc. Rockland, MA. January 2016.
6. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777-788.
7. National Multiple Sclerosis Society. Types of MS. Available at: https://www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed March 29, 2019.
8. Per clinical consultation with MS specialist, December 29, 2010.
9. Plegridy Prescribing Information. Biogen Idec Inc. Cambridge, MA. December 2018.
10. Aubagio Prescribing Information. Genzyme Corporation. Cambridge, MA. October 2018.
11. Gilenya Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. January 2019.
12. Tecfidera Prescribing Information. Biogen Idec Inc. Cambridge, MA. June 2018.
13. Lemtrada Prescribing Information. Genzyme Corporation. Cambridge, MA. January 2019.
14. Glatopa Prescribing Information. Sandoz Inc. Princeton, NJ. October 2018.
15. Zinbryta Prescribing Information. Abbvie. Cambridge, MA. July 2018.
16. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009; Oct;66(4):460-71.
17. Ocrevus Prescribing Information. Genentech, Inc. San Francisco, CA. November 2018.
18. Mayzent Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. March 2019.
19. Mavenclad Prescribing Information. EMD Serono, Inc. Rockland, MA. April 2019.

Nevada Medicaid

Multiple Sclerosis Agents
Fee for Service
October 1, 2018 - September 30, 2019

Drug Name	Count of Members	Count of Claims	Days Supply	Total Qty
AMPYRA	8	60	1,800	3,600
AUBAGIO	19	115	3,348	3,348
AVONEX	5	17	476	17
AVONEX PEN	7	52	1,456	52
BETASERON	1	7	196	98
COPAXONE	18	87	2,391	1,338
DALFAMPRIDINE ER	7	26	780	1,560
GILENYA	4	37	1,110	1,110
GLATIRAMER ACETATE	1	6	170	72
GLATOPA	1	2	56	24
LEMTRADA	4	10	39	14
OCREVUS	46	83	837	1,900
PLEGRIDY	1	13	364	13
REBIF	7	50	1,360	300
REBIF REBIDOSE	3	5	140	30
REBIF REBIDOSE TITRATION PACK	2	2	56	8
TECFIDERA	40	248	7,477	14,954
TECFIDERA STARTER PACK	9	9	270	540
TYSABRI	28	195	1,344	2,925



CC. Ampyra® (dalfampridine)

Therapeutic Class: Agents for the treatment of Neuromuscular Transmission Disorder
Last Reviewed by the DUR Board: July 25, 2013

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

1. Coverage and Limitations

Approval for Ampyra® (dalfampridine) will be given if all of the following criteria are met and documented:

a. Ampyra® (dalfampridine)

The recipient must meet all of the following:

1. The recipient must have a diagnosis of Multiple Sclerosis; 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.

2. Prior Authorization Guidelines

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

b. Requests for continuation of therapy will be approved for one year.

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 the leading cause of disability in young and middle-aged people in developed areas of the world *(MS Coalition 2018)*. MS is characterized by repeated episodes of inflammation within the brain and spinal cord, resulting in injury to the myelin sheaths that surround and insulate nerves, and subsequently the nerve cell axons *(Goodin et al 2002)*. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for 80 to 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 10% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - 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 *(Goodin et al 2002, Sanvito et al 2011, National MS Society 2019[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 prior category of PRMS can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States have been diagnosed with MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is reported more frequently in women than in men *(National MS Society 2019[b])*.
- Diagnosis of MS requires evidence of damage in at least 2 separate areas of the CNS, evidence of damage that occurred at 2 separate time points at least 1 month apart, and that other possible diagnoses have been ruled out. The clinically isolated syndrome (CIS) includes 1 attack and objective evidence of 1 lesion *(Thompson et al 2018)*. Following CIS, the course of MS is variable. The inclusion of CIS in the spectrum of MS phenotypes with prospective follow-up of most such patients determining their subsequent disease phenotype was also recommended in the recent revision of the MS clinical course descriptions *(Lublin et al 2014)*.
- Disease-modifying therapies (DMTs) delay the development from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*. Evaluation includes an extensive patient 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 leads to damage to the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of DMTs to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018[b])*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recently updated their guidelines on MS. Both guidelines recommend initiation of DMTs treatment early on in the patient's disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to the 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 (Corboy et al 2015, Goodin et al 2002, MS Coalition 2017, 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*). Tecfidera (dimethyl fumarate), Aubagio (teriflunomide), and Lemtrada (alemtuzumab) are all currently being evaluated in pediatric patients in Phase 3 trials.
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2019*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review

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

*A generic of teriflunomide received FDA-approval in 2018; however, a settlement agreement will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate); it is available in 20 mg/mL and 40 mg/mL injections. Mylan launched generic versions of the 20 mg/mL and the 40 mg/mL strengths of Copaxone on October 5, 2017.
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, Zinbryta (daclizumab) has been voluntarily withdrawn from the market by the manufacturer; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta. All references to the drug have been removed from this document.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
Ampyra (dalfampridine)	✔ *	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-
Avonex (IM interferon β-1a)	-	✔	✔	✔	✔	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	✔	✔	-
Copaxone/Glatopa	-	✔	-	-	-	-

Drug	Improve walking in MS‡	Relapsing forms of MS	Slow accumulation of physical disability	Decrease frequency of clinical exacerbations	First clinical episode	Progressive forms of MS
(glatiramer acetate)						
Gilenya (fingolimod)	-	✔ †	-	-	-	-
Lemtrada (alemtuzumab)	-	✔ ‡ (3rd line)	-	-	-	-
Mavenclad (cladribine)		✔				✔ §
Mayzent (siponimod)		✔			✔ ‖	✔ ‖
mitoxantrone	-	✔ (2nd line)	✔ (neurologic disability)	✔	-	✔ ¶
Ocrevus (ocrelizumab)	-	✔	-	-	-	✔ #
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-
Rebif (interferon β-1a)	-	✔	✔	✔	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-
Tysabri (natalizumab)	-	✔ **	-	-	-	-

IM=intramuscular; SC=subcutaneous
*Ampyra is indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.
†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
§ 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.
‖ Mayzent is a sphingosine-phosphate receptor modulator indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults.
¶Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications.
#Ocrevus is approved for PPMS.
**Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML) (a rare, but often fatal demyelinating disease of the central nervous system caused by the John Cunningham virus [JCV]). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation that 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 2017, Aubagio 2016, Avonex 2016, Betaseron 2018, Copaxone 2018, Extavia 2016, Gilenya 2018, Glatopa 2018, Lemtrada 2017, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Novantrone 2012, Ocrevus 2017, Plegridy 2018, Rebif 2015, Tecfidera 2018, Tysabri 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

- In the management of MS, numerous clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses 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 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)*. The results of several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg intramuscular [IM] once weekly) may be less efficacious while being more tolerable compared to higher dose Rebif (IFNβ-1a subcutaneous [SC] 3 times weekly or every other day) or glatiramer acetate *(Khan et al 2001[a], Khan et al 2001[b], Barbero et al 2006, Durelli et al 2002, Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing 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 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 first-line therapy is safe and effective *(Caon et al 2006, Zwibel 2006, Carra et al 2008)*. Patients switching to glatiramer acetate after experiencing inadequate response to IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.

- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- Glatiramer acetate 20 mg daily and 40 mg 3 times weekly have not been directly compared for efficacy. 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 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 than 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-weight 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. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio were evaluated in two Phase 3, randomized, double-blind, placebo-controlled trials – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (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 were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

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

treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab 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 randomized, Phase 3, open-label trials 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 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 *(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 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[a], 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 administered by SC injection 3 times per week) in 1656 patients with RMS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
  - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
  - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif across both trials (primary endpoint).
    - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
    - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
  - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
  - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
    - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; $p < 0.001$)
    - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; $p < 0.001$)
  - The most common adverse events 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) (*FDA Medical and Summary Reviews 2017*).
  - The percentages of patients with 12-week confirmed disability progression (primary endpoint) were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; $p = 0.03$).
  - The percentages of patients with 24-week CDP (secondary endpoint) were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; $p = 0.04$).
  - Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.

- The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
- From 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 trial, EXPAND was a double-blind, randomized, parallel-group, placebo-controlled, time-to-event study in patients with SPMS who had evidence of disability progression in the previous 2 years (*Bar-Or et al 2018, Fox et al 2015, 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 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 trial 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 both in the 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.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the

walking speed by about 25% in approximately one-third of MS patients as measured by the timed 25-foot walk (T25FW) *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- Avonex (IFNβ-1a IM) and Betaseron (IFNβ-1b) are FDA-approved for the treatment of the first clinical episode with MRI features consistent with MS. Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
- In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a 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 clinically definite multiple sclerosis (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 progressive-relapsing MS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd

enhancement or at month 12 for the number of lesions on T2 weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data including cohort data for mitoxantrone. Evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.

- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS, and due to being off-label, these uses are not included in Table 2. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. The ASCEND trial evaluated natalizumab in SPMS was found to have 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

- Patient 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 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[b]*).

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)*.
- RCTs (n = 39) evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, 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 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 disease-modifying drugs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment, detection of side effects, and capacity to address them properly. (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 disease-modifying drugs 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 effective to the 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 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, and precautions of use, 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 disease-modifying drugs, 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 disease-modifying drugs, 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 disease-modifying drugs, perform 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)
  - In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (Weak)
  - Consider continuing a disease-modifying drug if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
  - Advise all women of childbearing potential that disease-modifying drugs 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; or 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)

- 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 use 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)
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- With an increasing number of options for the treatment of RRMS, the place in therapy for an individual agent is not straightforward. Treatment decisions will likely be based on a consideration of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences. The 2015 AAN position statement supports access to all DMT for patients with MS. In addition, step therapy should be driven by evidence-based clinical and safety information and not just based on costs. Highly individualized treatment decisions are necessary for patients with MS according to the AAN *(Corboy et al 2015)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including pegIFN), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- In September 2018, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing or primary progressive MS, regardless of the person's age; for individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded; and for individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS.

- 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.
- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
  - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
  - 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.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) is associated with influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic 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, and urticaria immediately following injection. Injection site reactions including lipodystrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod was originally approved with a risk evaluation and mitigation strategies program (REMS) to inform healthcare providers about the serious risks including bradyarrhythmia, atrioventricular block, infections, macular edema, respiratory effects, hepatic effects, fetal risk, increased blood pressure, basal cell carcinoma, immune system effects following discontinuation, and hypersensitivity reactions; however, the FDA lifted the REMS requirements in November 2016. Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, in patients treated with fingolimod. Cases of PML

have occurred in the postmarketing setting in patients who were treated with fingolimod for at least 2 years. A warning for PML has been added to the fingolimod labeling; at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. 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.

- Teriflunomide is contraindicated in patients with severe hepatic impairment; patients who are pregnant, of childbearing potential, or that are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include risk of leukopenia, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels over 2 weeks. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate has no contraindications, except in patients with hypersensitivity to dimethyl fumarate or any excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury reported in the post-marketing setting. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following dimethyl fumarate therapy. 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 temporary dose reduction to 120 mg twice daily may reduce flushing.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10%) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort hypersensitivity reaction to natalizumab. 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, acute retinal necrosis, increased risk of infections (including opportunistic infections), and hepatotoxicity, diarrhea (not otherwise specified), and rash.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies. Alemtuzumab is only available through a restricted distribution and REMS program which requires the member, provider, pharmacy and infusion facility to be certified by the REMS program. Approximately one-third of patients who receive alemtuzumab develop thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. 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. Recent updates to the safety labeling include a warning that patients taking alemtuzumab are at risk for serious infections caused by *Listeria monocytogenes*. Patients that are prescribed alemtuzumab should be counseled about this risk, and to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should undergo tuberculosis screening according to local guidelines.

- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with RMS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with RMS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine can cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, 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 atrioventricular (AV) block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include 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 10 days after stopping siponimod due to fetal risk. The most adverse events are headache, hypertension, and transaminase increases.
- 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 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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 severe renal impairment (CrCl ≤ 50 mL/min). Based on animal data, dalfampridine may cause fetal harm.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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 until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, 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.
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:	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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.	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 heart rate < 45 bpm, atrioventricular (AV) block, or if lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course 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 treatments 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); and a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter). Conduct baseline and yearly 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 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 divided into 2 treatment cycles:	The use of Mavenclad in patients weighing less than 40 kg has not been investigated. Mavenclad is contraindicated in pregnant women and in female/males of reproductive

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			• First course/first cycle: start anytime • First cycle/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.	potential that do not plan to use effective contraception. The safety and effectiveness in pediatric patients have not been established.
Mayzent (siponimod)	Tablets: starter pack of tablets	Oral	Once daily	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 congestive heart failure develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop.	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of > 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3. Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Liver function tests should be monitored prior to each course of therapy.	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 6 weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection	SC	Every 14 days Titration: Start with 63 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 sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms.

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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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.

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

CONCLUSION

- DMTs for MS have shown benefits in patients with RRMS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite RRMS begin DMTs *(MS Coalition 2017)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2017)*. 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 the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products including Plegridy. With IFNβ, use caution in patients with depression or other mood disorders. Peginterferon β-1a every 2 weeks has demonstrated efficacy in reducing the ARR in relapsing forms of MS compared to placebo. Potential advantages of Plegridy are less frequent administration every 2 weeks and possibly the reduced risk of NAb development. 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 perceived inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(Corboy et al 2015, MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. Premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 5 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. The 2 new agents are Mavenclad (cladribine) and Mayzent (siponimod). Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence to their drug regimen *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and tolerability profiles. The oral products have not been compared to one another in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod, indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive

disease. 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.

- 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*). Lymphopenia is the most common adverse effect.
- 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 or new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) *(O'Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.

- Tysabri (natalizumab) has demonstrated very high efficacy vs placebo and although PML is a major safety concern, the overall incidence of PML has remained low (0.4%). 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)*.
  - The approval of Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of RMS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is, therefore, reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.

- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.

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Publication Date: May 6, 2019

Prior Authorization Guideline

Guideline Name Zelnorm (tegaserod)

1 . Indications

Drug Name: Zelnorm (tegaserod)
Irritable bowel syndrome with constipation Indicated for the treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C). Limitations of Use: The safety and effectiveness of Zelnorm in men with IBS-C have not been established.

2 . Criteria

Product Name: Zelnorm	
Approval Length	6 weeks [A]
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of irritable bowel syndrome with constipation (IBS-C)

AND

2 - Patient is female

AND

3 - Age less than 65 years [B]

AND

4 - Trial and failure, contraindication, or intolerance to ONE of the following: [C]

- Lactulose
- Polyethylene glycol

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

Approval Criteria

1 - Documentation of positive clinical response to therapy

3 . Endnotes

A. Authorization limit was set to 6 weeks because Zelnorm should be discontinued in patients who have not had adequate control of symptoms after 4 to 6 weeks of treatment. [1]
B. Zelnorm was removed from the market in 2007 due to evidence of increased risk of heart attacks and strokes but has been re-released after limiting the indication to adult women with IBS-C who are < 65 years of age to define a patient population with low cardiovascular risk. [2]
C. Osmotic laxatives should be tried/failed first before patients are placed on other therapies due to the favorable tolerability profile. [3]

4 . References

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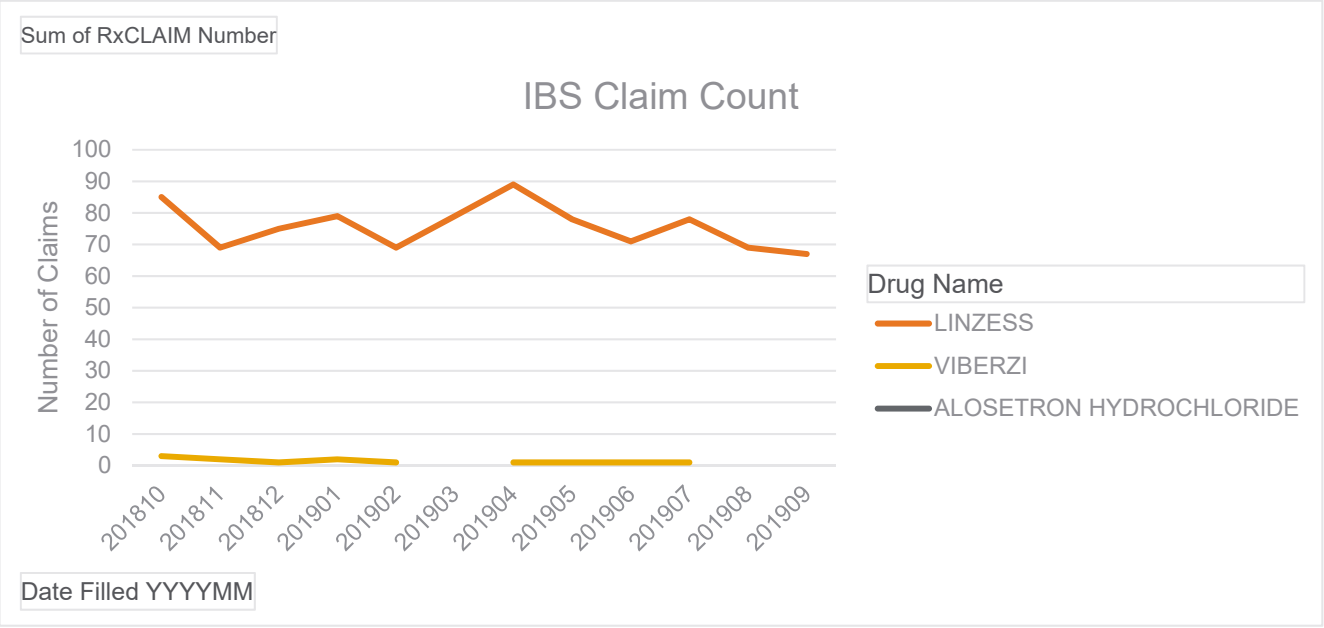
Nevada Medicaid

Irritable Bowel Syndrome Agents
Fee for Service
October 1, 2018 - September 30, 2019

Drug Name	Count of Members	Count of Claims	Days Supply	Total Qty
ALOSETRON HYDROCHLORIDE	1	1	30	60
LINZESS	221	908	36,020	36,140
VIBERZI	4	15	570	960



WW. Irritable-Bowel Syndrome Agents

Therapeutic Class: Irritable-Bowel Syndrome Agents
Trulance® last reviewed by the DUR Board: July 26, 2018
Last Reviewed by the DUR Board: July 28, 2016
Viberzi® last reviewed by the DUR Board April 28, 2016

Irritable-Bowel Syndrome Agents are subject to prior authorization and quantity limits based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

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

      1. The recipient is 18 years of age or older; and

      2. The requested agent is being prescribed based on FDA approved guidelines; and

         a. For requests for a diagnosis of Irritable-Bowel Syndrome with Constipation (IBS-C):

            1. For requests for Amitiza® (lubiprostone), the recipient must be female.

            2. The requested dose is appropriate based on indication and age.

               a. Linzess® (linaclotide): 290 µg daily.

               b. Amitiza® (lubiprostone): 16 µg daily.

               c. Trulance® (plecanatide): 3 µg daily.

         b. For requests for a diagnosis of Irritable-Bowel Syndrome with Diarrhea (IBS-D):

            1. The medication is being prescribed by or in consultation with a gastroenterologist; and

            2. The requested dose is appropriate based on indication and age.

               a. Lotronex® (alosetron): 0.5 mg twice daily or 1 mg twice daily.

b. Viberzi® (eluxadoline): 75 mg twice daily or 100 mg twice daily.

c. Xifaxan® (rifaximin): 550 mg three times a day for 14 days.

2. Prior Authorization Guidelines

a. Prior authorization approval will be given for an appropriate length of therapy based on the requested agent and diagnosis, not to exceed one year.

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

INTRODUCTION

Irritable bowel syndrome (IBS)

- IBS is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (*Wald 2019a*).
- IBS may consist of diarrhea-predominant (IBS-D; abnormal BMs are usually diarrhea), constipation-predominant (IBS-C; abnormal BMs are usually constipation), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (*Ford et al 2018, Wald 2019b*).
- IBS is a functional disorder of the gastrointestinal tract characterized by symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (*Andresen et al 2008, Ford et al 2009, Quigley et al 2012, World Gastroenterology Organization [WGO] 2015*).
- Prevalence estimates of IBS range from 10 to 12%, and it typically occurs in young adulthood (*Ford et al 2018*). IBS-D is more common in men, and IBS-C is more common in women (*WGO 2015*).
- Symptoms of IBS often interfere with daily life and social functioning (*WGO 2015*).
- The general goals of therapy in IBS are to alleviate the patient's symptoms and to target any specific exacerbating factors (eg, medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist (*Ford et al 2018*).
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (eg, beans, prunes, Brussel sprouts, bagels, etc.), and consumption of probiotics, as well as psychosocial therapies (eg, hypnosis, biofeedback, etc.) (*Ford et al 2018*).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include selective chloride channel activators (eg, Amitiza [lubiprostone]); guanylate cyclase-C agonists (eg, Linzess [linaclotide], Trulance [plecanatide]); mu-opioid receptor agonists (eg, Viberzi [eluxadoline]); poorly absorbable antibiotics (eg, Xifaxan [rifaximin]); serotonin-3 receptor antagonists (eg, Lotronex [alosetron]); antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); antispasmodics (eg, dicyclomine, hyoscine, etc.); select probiotics; and peppermint oil (*Ford et al 2018*).
- Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are Food and Drug Administration (FDA)-approved for the treatment of IBS-C in adults. Lubiprostone is indicated in women ≥ 18 years of age; tegaserod is indicated for the treatment of IBS-C in adult women < 65 years of age.
  - Tegaserod is a serotonin type 4 (5-HT_4) agonist FDA-approved in July 2002 for the short-term treatment of IBS-C in women and in August 2004 for the treatment of CIC in men and women < 65 years of age. In 2007, tegaserod was removed from the United States (U.S) market due to safety concerns based on a postmarketing pooled safety analysis of 29 clinical trials which demonstrated a higher rate of serious cardiovascular events (including angina, myocardial infarction and stroke) in patients treated with tegaserod vs placebo (*FDA Gastrointestinal Drugs Advisory Committee 2018, FDA Multi-Disciplinary Review [Zelnorm] 2019*).
  - In 2018, the FDA Gastrointestinal Drugs Advisory Committee evaluated the safety and efficacy of tegaserod and recommended approval of tegaserod for the treatment of female patients < 65 years of age with IBS-C at a low cardiovascular risk; tegaserod was re-introduced March 2019 (*Drugs@FDA 2019; FDA Gastrointestinal Drugs Advisory Committee 2018, FDA Multi-Disciplinary Review [Zelnorm] 2019*).
- Viberzi (eluxadoline) and Xifaxan (rifaximin) are FDA-approved for the treatment of IBS-D. Viberzi is a schedule IV controlled substance. Lotronex (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

Chronic idiopathic constipation (CIC)

- Amitiza (lubiprostone), Linzess (linaclotide), Motegrity (prucalopride), and Trulance (plecanatide) are indicated for the treatment of CIC. Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as < 3 bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (*American Gastroenterological Association [AGA] Medical Position Statement 2013, Bharucha et al 2013*).
  - Prucalopride, a selective 5-HT_4 receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility (*Shin et al 2014*).
  - The intestinal secretagogues, ie, lubiprostone, linaclotide, and plecanatide, exert their effects by increasing intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. There is no reported evidence indicating that these agents induce HAPCs.

Opioid-induced constipation (OIC)

- OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (*Brock et al 2012*). There are 4 products approved for use in OIC:
  - Amitiza (lubiprostone) is FDA-approved for the treatment of OIC in adults with chronic, non-cancer related pain.
  - Relistor (methylnaltrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. Relistor has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - Movantik (naloxegol) and Symproic (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORAs) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment, methylnaltrexone is suggested over no treatment, and there are no recommendations for the use of lubiprostone or prucalopride.

Traveler's diarrhea (TD)

- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. The disease is characterized by symptoms of loose stools and abdominal cramps. Although generally not serious, TD may result in inconveniences during travel, including changes to an itinerary, overseas medical encounters, and hospitalization (*Riddle et al 2017*).
  - For the prevention of TD, a 2017 guideline recommends prophylaxis with rifaximin in high-risk groups (eg, underlying health conditions); bismuth subsalicylate may be considered second-line in these situations. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

Hepatic encephalopathy (HE)

- HE is a common complication of severe liver disease. Neuropsychiatric abnormalities, ranging from shortened attention span to lethargy, confusion, and coma, are all possible manifestations depending on disease severity. At this time, pharmacological treatment is only recommended for patients with overt HE, which is diagnosed based on a clinical examination and use of the West Haven Criteria and the Glasgow Coma Score. Secondary prophylaxis of HE after an overt HE episode is also recommended, as is primary prophylaxis in high-risk patients with cirrhosis (*Vilstrup et al 2014*).
  - Rifaximin is FDA-approved for the reduction in risk of overt HE recurrence in adults. A joint guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) also recommend this agent as an adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).
- The scope of this review will focus upon Amitiza (lubiprostone), Linzess (linaclotide), Lotronex (alosetron), Motegrity (prucalopride), Movantik (naloxegol), Relistor (methylnaltrexone bromide), Symproic (naldemedine), Trulance (plecanatide), Viberzi (eluxadoline), Xifaxan (rifaximin), and Zelnorm (tegaserod) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (Motegrity, Trulance); Gastrointestinal Chloride Channel Activators (Amitiza); IBS Agents (Lotronex, Linzess, Viberzi, Zelnorm); Peripheral Opioid Receptor Antagonists (Movantik, Relistor, Symproic); Anti-infective Agents – Misc (Xifaxan)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amitiza (lubiprostone)	-
Linzess (linaclotide)	-
Lotronex (alosetron)	✔
Motegrity (prucalopride)	-
Movantik (naloxegol)	-
Relistor (methylnaltrexone bromide)	-
Symproic (naldemedine)	-
Trulance (plecanatide)	-
Viberzi (eluxadoline)	-
Xifaxan (rifaximin)	-
Zelnorm (tegaserod)	-

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

INDICATIONS

Table 2. FDA Approved Indications

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrex	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
Treatment of CIC in adults	✔	✔		✔				✔			
Treatment of OIC in adults with chronic, non-cancer pain	✔*				✔	✔	✔				
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation.	✔*				✔	✔	✔				
Treatment of OIC in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care						✔†					
Treatment of IBS-C in women ≥ 18 years of age	✔										
Treatment of IBS-C in adult women < 65 years of age											✔‡
Treatment of IBS-C in adults		✔						✔			
Treatment of IBS-D in adults									✔	✔	
Women with severe IBS-D who have: • chronic IBS symptoms (generally lasting 6 months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§			✔								
Reduction in risk of overt HE recurrence in adults										✔	

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
Treatment of TD caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age										✔ ||	

*Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.
† Injection formulation only. Use of Relistor beyond 4 months in the treatment of OIC in patients with advanced illness has not been studied.
‡The safety and efficacy of Zelnorm have not been established in men with IBS-C.
§ IBS-D is severe if it includes diarrhea and ≥ 1 of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.
|| Xifaxan should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

(*Prescribing information: Amitiza 2018, Linzess 2018, Lotronex 2016, Motegrity 2018, Movantik 2019, Relistor 2018, Symproic 2019, Trulance 2019, Viberzi 2018, Xifaxan 2018, Zelnorm 2019*)

- Lotronex was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of Lotronex to treat only women with severe IBS-D. Physicians are required to complete training before prescribing Lotronex to ensure that the benefits and risks of the agent are considered before administering it to patients (*Lotronex FDA press release 2016*).

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

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and CSBM frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (*Atluri et al 2014, Videlock et al 2013*). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; relative risk [RR] of failure to respond, 0.80; 95% CI, 0.76 to 0.85).
- A 2018 network meta-analysis compared the relative efficacy of the secretagogues linaclotide, lubiprostone, plecanatide, and tenapanor (not available in the U.S.) for the treatment of IBS-C in 15 randomized controlled trials (N = 8462). Linaclotide 290 mg once daily was ranked first in efficacy based on the FDA-recommended endpoint for IBS-C trials, abdominal pain, and CSBMs; plecanatide 6 mg once daily was ranked highest for safety (*Black et al 2018*).
  - The network meta-analysis was updated in 2019 to include 3 12-week Phase 3 randomized controlled trials evaluating the efficacy of tegaserod in 2472 female patients with IBS-C. For the FDA-recommended endpoint, all agents, including tegaserod, were significantly more effective than placebo, but linaclotide 290 mcg daily was ranked as the most effective for achieving at least a 30% improvement in abdominal pain along with an increase of at least 1 CSBM/week from baseline for at least 50% of treatment-weeks; tegaserod 6 mg twice a day was ranked third. Indirect comparison of active treatments showed no significant differences between individual drugs and dosages. (*Black et al 2019b*).
- A 2019 network meta-analysis that included 18 randomized controlled trials (N = 9844) compared the efficacy of alosetron, eluxadoline, ramosetron, and rifaximin in patients with IBS-D or IBS-M. All agents were found to be more effective than placebo. In an analysis that ranked agents based on their efficacy in improving both abdominal pain and stool consistency, effect on global symptoms of IBS, and effect on stool consistency, alosetron 1 mg twice daily was ranked highest (ie, most effective). Ramosetron 2.5 mcg once daily was ranked highest for relief from abdominal pain (*Black et al 2019a*).

- For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders. In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (*Drossman et al 2007, Drossman et al 2009, Johanson et al 2008b*).
- In 2 randomized, double-blind, placebo-controlled, 12-week studies, there were significantly more overall responders (based on improved abdominal pain and weekly CSBM from baseline) with plecanatide 3 mg vs placebo in patients with IBS-C (Study 1: 30% vs 18%; Study 2: 21% vs 14%) (*Trulance prescribing information 2019*).
- Three Phase 3 double-blind, placebo-controlled, multicenter, randomized controlled trials (301, 358, and 307) of similar design in 2470 adults patients evaluated the efficacy and safety of tegaserod vs placebo. In trial 301, treatment with tegaserod resulted in a statistically significant improvement in response rate vs placebo with a difference of 11.4% (95% CI, 3 to 30; p < 0.005). Trials 358 and 307 demonstrated treatment differences vs placebo of 4.7% and 5.3%, respectively, but results were not statistically significant. (*FDA Medical Review(s) [Zelnorm] 2002, FDA Multi-Disciplinary Review [Zelnorm] 2019, Müller-Lissner et al 2001, Novick et al 2002*).
- A systematic review of various therapies for the treatment of IBS included 1 systematic review of 11 RCTs (n = 9242) evaluating tegaserod vs placebo for the treatment of IBS-C. The outcome of proportion of patients with persistent IBS-C symptoms with tegaserod was 55% (3301/6041) vs 64% (2032/3201) with placebo. Treatment with tegaserod was shown to be superior vs placebo with an RR of 0.85 (95% CI, 0.80 to 0.90) with a number needed to treat (NNT) of 10 (95% CI, 8 to 14) (*Ford et al 2009, Ford and Vandvik 2012*).
- A 2004 systematic review and meta-analysis included 4 double-blind controlled trials (n = 3564) evaluating tegaserod in the treatment of IBS-C. In each trial, a statistically significant effect on constipation, abdominal pain/discomfort, bloating and global relief with tegaserod treatment was demonstrated in women, with the difference between placebo and tegaserod of 10 to 15%, primarily due to a high placebo response (*Lesbros-Pantoflickova et al 2004*).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (*Camilleri et al 2000, Camilleri et al 2001, Chey et al 2004, Lembo et al 2001, Lembo et al 2004, Rahimi et al 2008, Watson et al 2001*).
- A meta-analysis concluded that the 5-hydroxytryptamine type 3 (5-HT3) antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (*Andresen et al 2008*).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (*Cremonini et al 2003*).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in 2 randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 3 clinical trials in which 2427 patients with IBS-D (meeting Rome III criteria), average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and a Bristol Stool Scale (BSS) of 5.5 or greater with at least 5 days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (p = 0.01) and 25.1% of patients in the 100 mg group (p = 0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (p = 0.11) and 29.3% in the 100 mg group (p < 0.001) achieved the primary endpoint compared to 19% in the placebo group (*Lembo et al 2016a*).
- The safety and efficacy of eluxadoline for the treatment of IBS-D were also studied in patients with an inadequate response to loperamide in a randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 4 trial (n = 346). Patients with IBS-D (meeting Rome III criteria), average abdominal pain scores > 3 on a 0 to 10 scale during the week prior to randomization, a BSS of ≥ 5.5 with at least 5 days of BSS ≥ 5 during the week prior to randomization, and a self-reported inadequate response to loperamide within the previous year were randomized to eluxadoline 100 mg or placebo twice daily. The primary endpoint was the proportion of composite responders, defined as improvement in the daily worst abdominal pain score by 40% and < 5 BSS score for at least 50% of treatment days. Over the 12-week treatment period, significantly more eluxadoline- vs placebo-treated patients achieved the primary composite endpoint (22.7% vs 10.3%; p = 0.002) as well as the individual components of the endpoint (improvement in stool consistency [27.9% vs 16.7%; p = 0.01] and improvement in the daily worst abdominal pain score by 40% [43.6% vs 31.0%; p = 0.02]) (*Brenner et al 2019*).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in 3 double-blind, placebo-controlled trials.
  - In the first 2 trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg 3 times daily (n = 624) or placebo (n = 634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; $p < 0.05$; Trial 2: 47% vs 36%; $p < 0.01$ in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg 3 times daily (n = 328) or placebo (n = 308) for 2 additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; $p < 0.05$) (*ClinicalTrials.gov 2019, Lembo et al 2016b*).

IBS and CIC

- A 2018 systematic review and meta-analysis compared the efficacy of intestinal secretagogues (ie, linaclotide, lubiprostone, plecanatide, and tenapanor [currently under investigation for IBS-C]) for the treatment of chronic constipation or IBS-C (*Lasa et al 2018*). For patients with chronic constipation, intestinal secretagogues were superior to placebo for increasing the number of CSBMs per week (RR, 1.87; 95% CI, 1.24 to 2.83 [analysis included linaclotide, lubiprostone, and plecanatide]) and for achieving ≥ 3 SBMs per week (RR, 1.56; 95% CI, 1.31 to 1.85 [analysis included linaclotide and lubiprostone]). For those with IBS-C, intestinal secretagogues were superior to placebo for increase in CSBMs per week (RR, 2.44; 95% CI, 1.51 to 3.93 [analysis included linaclotide and tenapanor]) and for achieving ≥ 3 SBMs per week (RR, 1.97; 95% CI, 1.74 to 2.24 [analysis included linaclotide only).
- In a systematic review and meta-analysis, both linaclotide and plecanatide were efficacious for IBS-C and CIC compared to placebo. Diarrhea was more frequent with both drugs compared to placebo. In an indirect comparison, there were no differences between the 2 agents for efficacy in CIC, efficacy in IBS-C, frequency of diarrhea, or study withdrawal due to diarrhea (*Shah et al 2018*).
- A network meta-analysis of 13 RCTs evaluated the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in patients, predominantly women, ≥ 12 years of age (*Evans et al 2007*).
  - In patients with IBS-C, for the Subject Global Assessment (SGA) of relief in patients, tegaserod resulted in a statistically significant benefit in 2 trials, compared with a nonsignificant trend for benefit in the remaining 2 studies. For abdominal pain and discomfort, the RR for being a responder with tegaserod vs placebo was non-significant; for bowel habits (as measured by responder rate), 1 trial did not suggest a benefit with tegaserod, and 2 trials showed a nonsignificant trend in favor of tegaserod.
  - For patients with chronic constipation, the RR of being a responder in terms of CSBMs/week with tegaserod 12 mg vs placebo was 1.54 (95% CI, 1.35 to 1.75), with a weighted mean difference (WMD) of 0.6 (95% CI, 0.42 to 0.78). Differences between tegaserod and placebo in increases in BM frequency were small (< 1/week).

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥ 3 complete spontaneous bowel movements (CSBMs)/week compared with placebo with an RR of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥ 1 CSBM/week (RR, 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (*Nelson et al 2017*).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; $p < 0.001$) (*Li et al 2016*).
- A meta-analysis of 16 randomized controlled trials evaluated the safety and efficacy of prucalopride in the management of CIC (*Sajid et al 2016*). The primary outcome measure was the incidence of spontaneous bowel movements (SBMs) per week, and the secondary outcome measure was adverse events.
  - Based on data from 9 trials, prucalopride 2 mg significantly reduced the incidence of SBMs per week compared with placebo (standardized mean difference [SMD] 0.34; 95% CI, 0.11 to 0.56; $I^2 = 78\%$; $p = 0.003$).

- The risk of developing adverse events (eg, headache, abdominal cramps, excessive flatulence, dizziness, diarrhea, rash) was higher in the prucalopride 2 mg group (odds ratio [OR], 1.76; 95% CI, 1.33 to 2.34; I^2 = 53%; p < 0.0001). The majority of adverse events were reported within the first 24 hours of initiation of therapy and were transient.

- A systematic review and meta-analysis evaluated the efficacy of serotonin type 4 (5-HT_4) agonists, including prucalopride, velusetrag, and naronapride (not approved in the U.S.) for the treatment of CIC. 5-HT_4 agonists were superior to control for all measured outcomes (*Shin et al 2014*).
  - The proportion of patients randomized to a 5-HT_4 agonist who achieved a mean of ≥ 3 CSBMs per week was 27.5% vs 17.2% of patients randomized to control (RR, 1.85; 95% CI, 1.23 to 2.79; I^2 = 89%; p < 0.001).
  - Overall, 46.7% of patients randomized to a 5-HT_4 agonist achieved a mean increase of ≥ 1 CSBM per week over baseline vs 30.8% of control patients (RR, 1.57; 95% CI, 1.19 to 2.06; I^2 = 89%; p < 0.001).
  - 5-HT_4 agonists also showed significant improvement over control for patient-reported quality of life (QOL) measures.
  - Adverse events were more common with 5-HT_4 agonists than with control (RR, 1.25; 95% CI, 1.14 to 1.38) and included headache, diarrhea, nausea, and abdominal pain.
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (*Videlock et al 2013*).
- A double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that treatment with linaclotide 72 mcg improved the CSBM frequency over 12-weeks compared with placebo, with 13.4% of linaclotide-treated patients meeting responder requirements compared with 4.7% in the placebo group (95% CI, 1.8% to 5.2%) (*Schoenfeld et al 2018*).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (*Chey et al 2012*).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; p < 0.001; Study 2: 20.1% vs 12.8%; p = 0.004) (*DeMicco et al 2017, Miner et al 2017*).
- Six double-blind, placebo-controlled, multicenter, randomized controlled trials of similar design in adults (N = 2484) evaluated the safety and efficacy of prucalopride for the treatment of CIC in an integrated analysis of the results (*Camilleri et al 2016, Prucalopride FDA briefing document 2018).*
  - The percentage of patients with a mean frequency of ≥ 3 CSBMs/week over a 12-week treatment period was significantly higher with prucalopride 2 mg/day (27.8%) vs placebo (13.2%) (OR, 2.68; 95% CI, 2.16 to 3.33; p < 0.001); the NNT with prucalopride was 8.8 (95% CI, 7.1 to 11.6). Efficacy and safety outcomes were not significantly different between men and women.
  - The proportion of patients with a mean increase of ≥ 1 CSBM/week was 47.0% with prucalopride vs 29.9% with placebo (p < 0.001).
  - Out of the 6 trials, the 24-week trial failed to demonstrate statistical significance for the primary endpoint after both 12 and 24 weeks, causing moderate heterogeneity. The reasons for the smaller treatment effect in this study remain unclear.
  - Due to its differing mode of action, prucalopride may be beneficial for patients with CIC who have an insufficient quantity of high-amplitude propagating contractions (HAPCs) or in those who do not respond to other medications (*Camilleri et al 2016*).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥ 3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n = 274; n = 277) or placebo (n = 273; n = 276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2 mg experienced a significantly higher response compared to patients receiving placebo in both studies (COMPOSE-1 responders: 47.6% vs 34.6%; p = 0.002 and COMPOSE-2 responders: 52.5% vs 33.6%; p<0.0001, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (*Hale et al 2017*).

- COMPOSE-4 was a 2-week randomized, double-blind, placebo-controlled trial of naldemedine 0.2 mg in patients with OIC and cancer, and COMPOSE-5 was a 12-week, open-label extension study. In COMPOSE-4, there were significantly more SBM responders in the naldemedine group compared to placebo (71.1% vs 34.4%; p < 0.0001). Treatment-emergent adverse events were also higher with naldemedine vs placebo (44.3% vs 26.0%; p = 0.01). In the extension study, 80.2% of patients experienced a treatment-emergent adverse event, most commonly gastrointestinal adverse events (*Katakami et al 2017*).
- In a 2019 meta-analysis of 6 randomized controlled trials (N = 2762), naldemedine was superior to placebo in SBM response rate (OR, 3.00; 95% CI, 1.93 to 4.65), change in SBM frequency (OR, 6.46; 95% CI, 4.73 to 8.20), and change in complete SBM frequency (OR, 5.93; 95% CI, 4.90 to 6.96) (*Esmadi et al 2019*).
- A total of 1,300 patients were enrolled in 3, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥ 1 SBM improvement over baseline for all treatment weeks and ≥ 3 SBMs per week for at least 9 weeks of the 12-week study period. Lubiprostone (27.1%) had a significantly higher "overall responder rate" than placebo (18.9%; p = 0.03) (*Jamal et al 2015*). The primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week 8. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo (p = 0.004). In Study 3, the difference was not statistically significant; however, Study 3 was the only study that enrolled patients who received diphenylheptane opioids such as methadone. Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as < 3 SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n = 210) or placebo (n = 218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week 8. Changes from baseline in SBM frequency rates were significantly higher at week 8 (p = 0.005) and overall (p = 0.004) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (*Cryer et al 2014*).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments, including methylnaltrexone, naloxone, and alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (*Ford et al 2013*).
- In 2014, another systematic review of 21 randomized clinical trials evaluated 7 pharmacological treatments for OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within 4 hours, and time to first BM. Methylnaltrexone showed improvements in all 3 OOMs. Randomized controlled trials with naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. CB-5945 (not FDA-approved) and prucalopride (not FDA-approved for OIC) tended to increase BM frequency, especially with doses of 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (*Siemens et al 2015*).
- The efficacy of naloxegol has been established in K4 and K5, 2 replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least 4 weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥ 3 SBMs per week and an increase of ≥ 1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (p = 0.001 and p = 0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (p = 0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (p = 0.2) (*Chey et al 2014*).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (p = 0.002) and with naloxegol 12.5 mg vs placebo (p = 0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (p = 0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (p < 0.001 for all comparisons).

- Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, centrally mediated analgesia was preserved.

- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxative effects similar to SBMs and predictable timing (*Bull et al 2015, Thomas et al 2008*). Similar findings have been reported in patients with OIC with chronic non-cancer pain (*Michna et al 2011, Webster et al 2017*).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of 4 weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with ≥ 3 SBMs per week, with an increase of ≥ 1 SBMs per week over baseline, for at least 3 weeks in the 4-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (p = 0.03 vs placebo), 51.5% (p = 0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (*Rauck et al 2017*).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubiprostone, naldemedine, naloxegol, subcutaneous (SC) and oral methylnaltrexone, and prucalopride (not FDA-approved for OIC) and alvimopan (not FDA-approved for OIC) (*Sridharan and Sivaramakrishan 2018*). Observations from 16 randomized controlled trials with 4048 patients demonstrated that lubiprostone, naldemedine, naloxegol, and SC and oral methylnaltrexone performed better vs placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with SC methylnaltrexone resulted in significantly improved RFBMs vs lubiprostone, naloxegol, and oral methylnaltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while SC methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.
- Another systematic review and network analysis of 27 studies found methylnaltrexone, naloxone, naloxegol, naldemedine, alvimopan, and lubiprostone significantly more efficacious than placebo for OIC (*Nee et al 2018*).
- A systematic review and network meta-analysis of 27 studies compared the efficacy and safety of methylnaltrexone, naloxone, naldemedine, naloxegol, lubiprostone, linaclotide, plecanatide, and several agents that are not currently approved in the U.S. in OIC. The authors found that when non-response was defined as a failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline or an average of ≥ 3 BMs per week, naloxone was the most efficacious treatment for OIC (RR, 0.65; 95% CI, 0.52 to 0.80) and the safest when ranked against other agents. When non-response was defined as only failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline, naldemedine was found to be the most efficacious (RR, 0.66; 95% CI, 0.56 to 0.77), followed by alvimopan (RR, 0.74; 95% CI; 0.57 to 0.94) (*Luthra et al 2018*).

TD

- Both a 2012 and 2017 meta-analysis including 4 and 5 randomized, placebo-controlled trials, respectively, demonstrated the superiority of rifaximin in preventing TD. In the 2012 analysis by *Alajbegovic et al*, rifaximin reduced the risk of disease by 67% (RR, 0.33; 95% CI, 0.24 to 0.45), while the 2017 analysis by *Ng et al* showed a 52.2% RR reduction (RR, 0.478; 95% CI, 0.375 to 0.610). Neither analysis reported any new safety signals (*Alajbegovic et al 2012* and *Ng et al 2017*).

HE

- Interventions for the treatment of overt HE were compared in a 2014 network meta-analysis of 20 randomized controlled trials (N = 10,007). Results showed no significant difference between neomycin and rifaximin when considering the outcomes of clinical improvement, blood ammonia concentration, and mental status. However, neomycin demonstrated an increased risk of adverse events when compared to rifaximin (OR, 14.03; 95% CI, 0.06 to 3035.53) (*Zhu et al 2015*).
- A 2019 meta-analysis evaluated whether the addition of rifaximin to lactulose improved outcomes in patients with overt HE. A total of 2276 patients were included across 5 randomized controlled trials and 5 observational studies. In a pooled analysis of data from all 10 studies, combination therapy improved efficacy (risk difference [RD], 0.26; 95% CI, 0.19 to 0.32) and reduced the risk of death (RD, -0.11; 95% CI, -0.19 to -0.03). Similar trends were seen in separate analyses that included only data from the randomized controlled trials. The risk of adverse events was similar between combination therapy and lactulose alone (RD, −0.06; 95% CI, −0.24 to 0.13) (*Wang et al 2019*).

CLINICAL GUIDELINES

IBS

- The 2018 American College of Gastroenterology (ACG) monograph on the management of IBS makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2018*):

- Recommends linaclotide, plecanatide, and lubiprostone for overall symptom improvement in patients with IBS-C (strong; high, moderate, and moderate quality of evidence rating, respectively).
- Suggests rifaximin for reduction in global IBS symptoms, as well as bloating in non-constipated patients (weak; moderate)
- Suggests alosetron for overall symptom improvement in female patients with IBS-D (weak; low quality).
- Suggests eluxadoline for overall symptom improvement in patients with IBS-D (weak; moderate).
- Recommends fiber for overall symptom improvement (strong; moderate).
- Antidepressants: Recommends TCAs for overall symptom improvement (strong; high quality); suggests SSRIs for overall symptom improvement (weak; low quality).
- Suggests against polyethylene glycol (PEG) and loperamide for overall symptom improvement.

- The AGA guideline on management of IBS makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Weinberg et al 2014*):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (*WGO, 2015*).

CIC

- The 2014 ACG monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2014*). Of note, only statements pertaining to CIC are included as the monograph on IBS management was updated in 2018:
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
  - Prucalopride is more effective than placebo in improving symptoms of CIC (strong; moderate)
  - Although supported by varying levels of evidence, fiber supplements, osmotic laxatives (PEG, lactulose), and stimulant laxatives (sodium picosulfate [not available in the U.S. as a single agent], bisacodyl) are recommended for the treatment of CIC (all Strong recommendations).
- Additional guidelines on the management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as “rescue agents”. Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*).

OIC

- For the management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative refractory OIC, naldemedine or naloxegol are recommended over no treatment. Methylnaltrexone is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low and costs may be prohibitive. The AGA does not make any recommendations for the use of lubiprostone or prucalopride for OIC due to lack of evidence.

TD

- Guidelines for TD were published in 2017 and recommend rifaximin for moderate-to-severe cases of the disease. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

HE

- A joint guideline from AASLD and EASL recommends rifaximin as an adjunct therapy to lactulose for the prevention of overt HE and recurrent episodes of HE after the second episode (*Vilstrup et al 2014*).

SAFETY SUMMARY

- Contraindications:
  - Amitiza is contraindicated with known or suspected mechanical gastrointestinal obstruction.
  - Lotronex has several contraindications, including a history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic

colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment.
  - Linzess and Trulance are contraindicated in patients age 6 years or younger and in patients with known or suspected mechanical gastrointestinal obstruction.
  - Motegrity is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, and severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum; and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Movantik is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong cytochrome (CYP) 3A4 inhibitors (eg, clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction.
  - Symproic is contraindicated in patients with a known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Viberzi has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than 3 alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected pancreatic duct obstruction; severe hepatic impairment; history of severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; use in patients without a gallbladder; or known hypersensitivity to the drug.
    - On March 15, 2017, the FDA warned that Viberzi should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (*FDA Drug Safety Communication 2017*). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
  - Xifaxan is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in Xifaxan.
  - Zelnorm is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment or end-stage renal disease; and moderate or severe hepatic impairment.
- Boxed Warnings:
  - Linzess and Trulance are contraindicated in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age.
  - Lotronex has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, Lotronex should be discontinued. Lotronex should be used only in female patients with severe IBS-D who have not benefited from usual therapies.
- Warnings/precautions:
  - Amitiza: nausea (29% incidence in CIC), diarrhea (12% in CIC), syncope and hypotension, dyspnea, and bowel obstruction
  - Motegrity and Zelnorm: Worsening of depression and emergence of suicidal thoughts and behavior may occur during therapy. Patients should discontinue the drug and contact their provider if these situations occur.
  - Movantik, Relistor, Trulance, and Zelnorm: Discontinue in the event of severe, persistent, or worsening abdominal pain or diarrhea.
  - Relistor and Symproic: Use with caution in patients with known or suspected lesions of the gastrointestinal tract; discontinue in the event of severe, persistent, or worsening abdominal pain.
  - Viberzi: Constipation, sometimes requiring hospitalization, has been reported following administration of Viberzi. Patients who develop severe constipation should discontinue treatment and contact their health care provider immediately.
  - Zelnorm: Avoid use in patients with severe diarrhea. Patients should contact their healthcare provider if severe diarrhea, hypotension or syncope occur.

- Drug Interactions
  - Amitiza: Diphenylheptane opioids such as methadone may interfere with the efficacy of Amitiza.
  - Lotronex: Clinically significant drug interactions associated with Lotronex include CYP1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine. Concomitant use of Lotronex and fluvoxamine is contraindicated.
  - Motegrity: Concomitant administration of Motegrity and erythromycin may increase erythromycin concentrations via an unknown mechanism. Concomitant administration of Motegrity and ketoconazole may increase the Motegrity concentrations.
  - Movantik: Concomitant use of Movantik should be avoided with the following drug classes: moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (eg, rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of Movantik is warranted.
  - Relistor: Concomitant use of Relistor with other opioid antagonists should be avoided due to potentially additive effects that may increase the risk of opioid withdrawal.
  - Symproic: Concomitant use of Symproic should be avoided with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (eg, fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (eg, amiodarone, captopril, cyclosporine, quinidine, verapamil) can increase Symproic concentrations.
  - Viberzi: Drug interactions with Viberzi which potentially may result in clinically relevant effects include the following drug classes: organic anion transporting polypeptide (OATP) 1B1 inhibitors (eg, cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (eg, ciprofloxacin, fluconazole, clarithromycin, paroxetine, bupropion), constipation-inducing drugs (eg, alosetron, anticholinergics, opioids), OATP1B1 and breast cancer resistance protein (BCRP) substrates (eg, rosuvastatin), and CYP3A substrates (eg, alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
  - Xifaxan: Concomitant administration of drugs that are P-glycoprotein inhibitors with Xifaxan can substantially increase systemic exposure to rifaximin. Caution should be exercised when concomitant use of Xifaxan and a P-glycoprotein inhibitor such as cyclosporine is needed.
- Risk Evaluation and Mitigation Strategy (REMS):
  - Lotronex has REMS that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (*FDA REMS program 2019*).
- Adverse events:
  - The IBS and constipation agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amitiza (lubiprostone)	Capsules	Oral	Treatment of CIC in adults and OIC: twice daily Treatment of IBS-C in women ≥ 18 years of age: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in moderate and severe hepatic impairment.
Linzess (linaclotide)	Capsules	Oral	IBS-C: once daily CIC: once daily	• Safety and efficacy have not been established in pediatric patients. • Capsule contents may be administered with applesauce or water if a patient is unable to swallow.
Lotronex (alosetron)	Tablets	Oral	Women with severe IBS-D: twice daily	• Pregnancy category B* • Safety and efficacy have not been established in pediatric patients.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Caution should be used in patients ≥ 65 years of age due to risk for constipation. • Caution should be used in patients with mild or moderate impairment; use should be avoided in severe hepatic impairment. • Treatment should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice daily.
Motegrity (prucalopride)	Tablets	Oral	CIC in adults: once daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted for severe renal impairment (CrCl < 30 mL/min).
Movantik (naloxegol)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube. • Tablets should be taken 1 hour before the first meal of the day or 2 hours after the meal. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Dose should be adjusted for renal impairment (CrCl < 60 mL/min). • Maintenance laxative therapy should be discontinued prior to initiating therapy. • Movantik should be discontinued when opioid pain medication is discontinued.
Relistor (methylnaltrex-one)	Single-use vials, single-use pre-filled syringes, tablets	Oral, SC injection	OIC in chronic non-cancer pain: SC injection once daily, or oral tablet(s) once daily in the morning OIC in advanced illness: Weight-based SC injection once every other day, as needed (maximum of once daily)	• Safety and efficacy have not been established in pediatric patients. • SC injection should be administered in the upper arm, abdomen, or thigh; injection sites should be rotated. • Oral dose should be adjusted in moderate and severe hepatic impairment; adjustment of SC injection dose should be considered in severe hepatic impairment. • Dose should be adjusted in moderate to severe renal impairment. • Maintenance laxative therapy should be discontinued prior to initiating therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Tablets should be taken with water 30 minutes before the first meal of the day. • Relistor should be discontinued when opioid pain medication is discontinued.
Symproic (naldemedine)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Symproic should be discontinued when opioid pain medication is discontinued.
Trulance (plecanatide)	Tablets	Oral	CIC and IBS-C: once daily	• Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube.
Viberzi (eluxadoline)	Tablets	Oral	Treatment of IBS-D in adults: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in patients who are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).
Xifaxan (rifaximin)	Tablets	Oral	IBS-D: 3 times daily for 14 days TD: 3 times daily for 3 days Hepatic encephalopathy: twice daily	• Safety and efficacy have not been established in pediatric patients < 12 years of age with TD or patients < 18 years of age for hepatic encephalopathy and IBS-D. • Patients with IBS-D who experience recurrence may be retreated up to 2 times with the same regimen. • Should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.
Zelnorm (tegaserod)	Tablets	Oral	IBS-D: twice daily	• Tablets should be taken 30 minutes before a meal. • Zelnorm should be discontinued if no response is seen after 4 to 6 weeks of treatment.

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

See the current prescribing information for full details.

CONCLUSION

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- IBS is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (*Andresen et al 2008, Ford et al 2018, Quigley et al 2012, WGO 2015*). IBS has 4 subtypes depending on the change in bowel habits: IBS-D, IBS-C, IBS-M, or IBS-U.
  - Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (*Andresen et al 2008, Ford et al 2009*).
  - Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are indicated for the treatment of IBS-C. Amitiza is a selective chloride channel activator, and Linzess and Trulance are guanylate cyclase-C agonists. Zelnorm is a 5-HT_4 agonist that was re-introduced to the market in March 2019.
  - Lotronex (alosetron), Viberzi (eluxadoline), and Xifaxan (rifaximin) are indicated for the treatment of IBS-D.
    - Viberzi is a mu-opioid receptor agonist and a schedule IV controlled substance.
    - Xifaxan is a rifamycin antibacterial. Patients with IBS-D who experience recurrence with Xifaxan treatment may be retreated up to 2 times with the same regimen.
    - Lotronex is limited to use in females with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, Lotronex has a boxed warning regarding risk of gastrointestinal adverse events including ischemic colitis, and also has a REMS program.
  - The 2018 ACG monograph on the management of IBS strongly recommends that Linzess and Amitiza are superior to placebo for the treatment of IBS-C, and Trulance is effective in IBS-C; they weakly recommend that Xifaxan is effective in reducing IBS symptoms and bloating in IBS-D, Lotronex is effective in females with IBS-D, and Viberzi is superior to placebo in IBS-D (*Ford et al 2018*).
- The 2014 ACG monograph on the management of CIC and IBS notes that linaclotide and lubiprostone are each effective for the treatment of CIC, and prucalopride is more effective than placebo in improving symptoms of CIC (*Ford et al 2014*).
  - Additional guidelines on management of constipation suggest increased fiber intake and osmotic laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*). Stimulant laxatives are to be used as needed or as "rescue agents." Amitiza and Linzess can be considered when symptoms of constipation do not respond to laxatives.
  - Amitiza, Linzess, Motegrity (prucalopride), and Trulance are indicated for the treatment of CIC.
  - Motegrity is a selective 5-HT_4 receptor agonist that stimulates colonic peristalsis. Amitiza, Linzess, and Trulance are intestinal secretagogues and there is no reported evidence indicating that these agents induce peristalsis.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative refractory OIC, Symproic (naldemedine) or Movantik (naloxegol) are recommended over no treatment. Relistor (methylnaltrexone) is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low. The AGA does not make any recommendations for the use of Amitiza or Motegrity for OIC due to lack of evidence.
  - Amitiza, Movantik, Relistor, and Symproic are approved for treatment of OIC in patients with chronic non-cancer pain, and in those chronic pain related to prior cancer or its treatment in those who do not require frequent (eg, weekly) opioid dosage escalation. Relistor injection is also approved in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.
  - Movantik, Relistor, and Symproic are PAMORAs.
- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. For the prevention of TD, guidelines recommend prophylaxis with rifaximin in high-risk groups. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).
- HE is a common complication of severe liver disease characterized by neuropsychiatric abnormalities that vary in presentation based on disease severity. The AASLD and EASL recommend rifaximin as adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).

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Publication Date: September 11, 2019

Prior Authorization Guideline

Guideline Name Nucala (mepolizumab)

1 . Indications

Drug Name: Nucala (mepolizumab)

Indications

Maintenance Treatment of Severe Asthma Indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

Eosinophilic Granulomatosis with Polyangiitis Indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

2 . Criteria

Product Name: Nucala

Diagnosis	Severe Asthma
Approval Length	6 Months [G]
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of severe asthma [1, A]

AND

2 Asthma is an eosinophilic phenotype as defined by one of the following [1, 3, B]:

- Baseline (pre-treatment) peripheral blood eosinophil level greater than or equal to 150 cells/microliter
- Peripheral blood eosinophil levels were greater than or equal to 300 cells/microliter within the past 12 months

AND

3 One of the following:

3.1 Patient has had at least one or more asthma exacerbations requiring systemic corticosteroids within the past 12 months [2-4, H]

OR

3.2 Any prior intubation for an asthma exacerbation

OR

3.3 Prior asthma-related hospitalization within the past 12 months

AND

4 Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications [2-4, D]:

4.1 Both of the following:

- High-dose inhaled corticosteroid (ICS) (e.g., greater than 500 mcg fluticasone propionate equivalent/day)
- Additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist [LABA], theophylline)

OR

4.2 One maximally-dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

5 Age greater than or equal to 12 years [1]

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Nucala

Diagnosis	Severe Asthma
Approval Length	12 Months
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Documentation of positive clinical response to therapy (e.g., reduction in exacerbations, improvement in forced expiratory volume in 1 second [FEV1], decreased use of rescue medications) [C]

AND

2 Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications [2-4]:

2.1 Both of the following:

- Inhaled corticosteroid (ICS) [5, E]
- Additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist [LABA], theophylline)

OR

2.2 A combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Nucala

Diagnosis	Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Approval Length	12 Months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)

AND

2 Patient's disease has relapsed or is refractory to standard of care therapy (i.e., corticosteroid treatment with or without immunosuppressive therapy) [F, 7]

AND

3 Patient is currently receiving corticosteroid therapy (e.g., prednisolone, prednisone) [F, 7]

AND

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

- Pulmonologist
- Rheumatologist
- Allergist/Immunologist

Product Name: Nucala

Diagnosis	Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Approval Length	12 Months
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Documentation of positive clinical response to therapy (e.g., increase in remission time)

3 . Endnotes

A. Patients included across the 3 pivotal studies (DREAM, MENSA, and SIRIUS) [2-4] were characterized with clinical features of severe refractory asthma per American Thoracic Society (ATS) criteria [5]. Per the ATS: "Severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.’’ This definition includes patients who received an adequate trial of these therapies in whom treatment was stopped due to lack of response. In patients greater than 6 years of age, ‘‘Gold Standard/International Guidelines treatment’’ is high dose ICS plus a long-acting beta 2-agonist (LABA), leukotriene modifier or theophylline and/or continuous or near continuous systemic corticosteroids as background therapy."
B. Inclusion criteria was modified from the DREAM study to the MENSA study to be limited to patients with eosinophils greater than or equal to 150 cells/mcL in the peripheral blood at screening or greater than or equal to 300 cells/mcL at some time during the previous year [3].
C. The primary endpoint for the DREAM and MENSA studies was the annual rate of clinically significant asthma exacerbations as a composite of the required use of systemic corticosteroids for at least 3 days, admission, or ED visit. Both studies showed mepolizumab-treated patients experienced a significant improvement in exacerbation rates compared with baseline and compared with placebo. [2, 3]
D. The 2017 Global Strategy for Asthma Management and Prevention update lists anti-interleukin- 5 treatment as an add on option for patients 12 years of age or older with severe eosinophilic asthma that is uncontrolled on two or more controllers plus as-needed reliever medication (Step 5 drugs) [6].
E. Asthma treatment can often be reduced, once good asthma control has been achieved and maintained for three months and lung function has hit a plateau. However the approach to stepping down will depend on patient specific factors (e.g., current medications, risk factors). At this time evidence for optimal timing, sequence and magnitude of treatment reductions is limited. It is feasible and safe for most patients to reduce the ICS dose by 25-50% at three month intervals, but complete cessation of ICS is associated with a significant risk of exacerbations [6].
F. Nucala was approved for Eosinophilic Granulomatosis with Polyangiitis (EGPA) based on the results from the pivotal, 52-week, Phase III MIRRA study. MIRRA looked at the efficacy and safety of 300 mg of mepolizumab administered SQ every four weeks versus

placebo as add-on therapy to standard of care (corticosteroids plus or minus immunosuppressants) in 136 patients with relapsing and/or refractory EGPA. MIRRA reported statistically significant outcomes with both co-primary endpoints (i.e., accrued time in remission and proportion of patients achieving remission) in favor of the treatment group [7, 8].

G. The 2018 Global Strategy for Asthma Management and Prevention update recommends that patients with asthma should be reviewed regularly to monitor their symptom control, risk factors and occurrence of exacerbations, as well as to document the response to any treatment changes. Ideally, patients should be seen 1-3 months after starting treatment and every 3-12 months thereafter. [6]
H. Per P&T Committee, February 2019, revised exacerbation requirement to mirror other IL-5 antagonists.

4 . References

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Prior Authorization Guideline

Guideline Name Dupixent (dupilumab)

1 . Indications

Drug Name: Dupixent (dupilumab)
Atopic Dermatitis Indicated for the treatment of patients aged 12 years and older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids. **Asthma** Indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitations of use: Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus. **Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)** Indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

2 . Criteria

Product Name: Dupixent	
Diagnosis	Atopic Dermatitis
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria	

1 - Diagnosis of moderate to severe atopic dermatitis [1]

AND

2 - One of the following: [3, 5-6]

2.1 Trial and failure, contraindication, or intolerance to ONE medium to high potency topical corticosteroid (e.g., betamethasone, triamcinolone)

OR

2.2 Trial and failure or intolerance to one of the following, unless the patient is not a candidate for therapy (e.g., immunocompromised)

- Elidel (pimecrolimus) topical cream
- tacrolimus topical ointment

AND

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

- Dermatologist
- Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Atopic Dermatitis
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to Dupixent therapy (e.g., reduction in body surface area involvement, reduction in pruritus severity)

Product Name: Dupixent	
Diagnosis	Eosinophilic Asthma
Approval Length	6 Months [D]

Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of moderate to severe asthma

AND

2 - Asthma is an eosinophilic phenotype as defined by a baseline (pre-treatment) peripheral blood eosinophil level greater than or equal to 150 cells per microliter [A]

AND

3 - Age greater than or equal to 12 years [1]

AND

4 - One of the following:

4.1 Patient has had at least one or more asthma exacerbations requiring systemic corticosteroids within the past 12 months [7, 8]

OR

4.2 Any prior intubation for an asthma exacerbation [B]

OR

4.3 Prior asthma-related hospitalization within the past 12 months [7, 8, B]

AND

5 - Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

5.1 Both of the following [7, 8, 10]:

- High-dose inhaled corticosteroid (ICS) [e.g., greater than 500 mcg fluticasone propionate equivalent/day]
- Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]

OR

5.2 One maximally-dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Eosinophilic Asthma
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to therapy (e.g., reduction in exacerbations, improvement in FEV1, decreased use of rescue medications)

AND

2 - Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

2.1 Both of the following [7, 8, 10]:

- Inhaled corticosteroid (ICS) [11, C]
- Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]

OR

2.2 A combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Oral Corticosteroid Dependent Asthma
Approval Length	6 Months [D]
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of moderate to severe asthma

AND

2 - Age greater than or equal to 12 years [1]

AND

3 - Patient is currently dependent on oral corticosteroids for the treatment of asthma

AND

4 - Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

4.1 Both of the following [9]:

- High-dose inhaled corticosteroid (ICS) [e.g., greater than 500 mcg fluticasone propionate equivalent/day]
- Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]

OR

4.2 One maximally-dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Oral Corticosteroid Dependent Asthma
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to Dupixent therapy (e.g., reduction in exacerbations, improvement in FEV1, reduction in oral corticosteroid dose)

AND

2 - Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

2.1 Both of the following [7, 8, 10]:

- Inhaled corticosteroid (ICS) [11, C]
- Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]

OR

2.2 A combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

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

- Pulmonologist
- Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
Approval Length	12 Month(s)
Therapy Stage	Initial Authorization

Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP)

AND

2 - Unless contraindicated, the patient has had an inadequate response to 2 months of treatment with an intranasal corticosteroid (e.g., fluticasone, mometasone) [Document drug(s), dose, duration and date of trial] [12, 13]

AND

3 - Dupixent will be used in combination with another agent for CRSwNP (e.g., intranasal corticosteroid)

AND

4 - Prescribed by or in consultation with an Allergist/Immunologist

Product Name: Dupixent	
Diagnosis	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to therapy (e.g., reduction in nasal polyps score [NPS; 0-8 scale], improvement in nasal congestion/obstruction score [NC; 0-3 scale])

AND

2 - Dupixent will be used in combination with another agent for CRSwNP (e.g., intranasal corticosteroid)

AND

3 - Prescribed by or in consultation with an Allergist/Immunologist

3 . Background

Clinical Practice Guidelines

Table 1. Relative potencies of topical corticosteroids [3]

Class	Drug	Dosage Form	Strength (%)
Very high potency	Augmented betamethasone dipropionate	Ointment, gel	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
High Potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream, lotion	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment, lotion	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream, lotion	0.1
	Triamcinolone acetonide	Cream, ointment, lotion	0.1
Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

4 . Endnotes

A. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils greater than or equal to 150 cells/mcL. In subjects with baseline blood eosinophil count less than 150 cells/mcL, similar severe exacerbation rates were observed between Dupixent and placebo. [1]
B. Recommendation inferred from the national P&T committee meeting, December 2015, regarding similar agent first-in-class IL-5 antagonist Nucala (mepolizumab) in the use of severe eosinophilic asthma.

C. Asthma treatment can often be reduced, once good asthma control has been achieved and maintained for three months and lung function has hit a plateau. However the approach to stepping down will depend on patient specific factors (e.g., current medications, risk factors). At this time evidence for optimal timing, sequence and magnitude of treatment reductions is limited. It is feasible and safe for most patients to reduce the ICS dose by 25-50% at three month intervals, but complete cessation of ICS is associated with a significant risk of exacerbations [11].
D. The 2018 Global Strategy for Asthma Management and Prevention update recommends that patients with asthma should be reviewed regularly to monitor their symptom control, risk factors and occurrence of exacerbations, as well as to document the response to any treatment changes. Ideally, patients should be seen 1-3 months after starting treatment and every 3-12 months thereafter. The AS Trial 1 and 2 measured change in FEV1 at week 12. AS Trial 3 measured percentage reduction in oral corticosteroid dose at week 24. [1, 10]

5 . References

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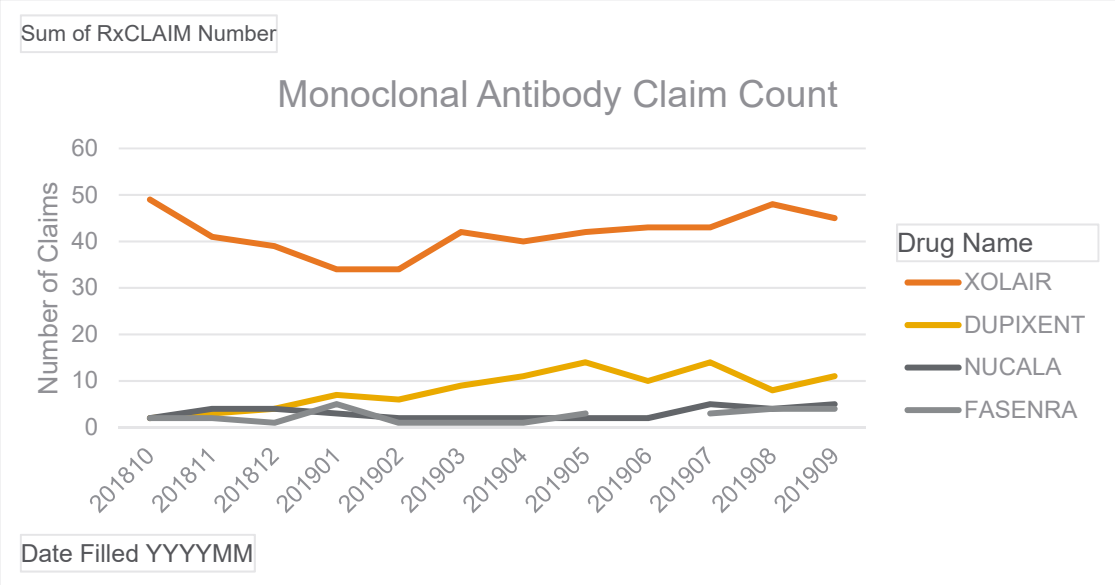
Nevada Medicaid

Monoclonal Antibodies for Asthma
Fee for Service
October 1, 2018 - September 30, 2019

Drug Name	Count of Members	Count of Claims	Days Supply	Total Qty
DUPIXENT	21	99	2,578	386
FASENRA	8	27	791	27
NUCALA	8	37	392	39
XOLAIR	57	500	10,260	4,892



P. Monoclonal Antibody Agents

Therapeutic Class: Respiratory Monoclonal Antibody Agents
Fasenra® reviewed by DUR Board: April 26, 2018
Xolair® previously reviewed: October 19, 2017
Last Reviewed by the DUR Board: July 28, 2016

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

1. Coverage and Limitations

A. Xolair® (Omalizumab)

1. The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies.

2. All of the following criteria must be met and documented for a diagnosis of moderate to severe persistent asthma:

a. The recipient must be six years of age or older; and

b. The recipient must have a history of a positive skin test or Radioallergosorbent (RAST) test to a perennial aeroallergen; and

c. The prescriber must be either a pulmonologist or allergist/ immunologist; and

d. The recipient must have had an inadequate response, adverse reaction or contraindication to inhaled, oral corticosteroids; and

e. The recipient must have had an inadequate response, adverse reaction or contraindication to a leukotriene receptor antagonist; and

f. The recipient must have had a pretreatment serum total Immunoglobulin E (IgE) level between 30 IU/mL and 700 IU/mL; and

g. The recipient's current weight must be recorded; and

h. The requested dose is appropriate for the recipient’s pre-treatment serum IgE and body weight (see Table 1).

3. All the following criteria must be met and documented for diagnosis of chronic idiopathic urticaria (CIU):

a. The recipient is 12 years of age or older; and

b. The recipient must have had an inadequate response, adverse reaction or contraindication to two different oral second generation antihistamines; and

c. The recipient must have had an inadequate response, adverse reaction or contraindication to an oral second generation antihistamine in combination with a leukotriene receptor antagonist; and

d. The prescriber must be either an allergist/immunologist, dermatologist or a rheumatologist or there is documentation in the recipient's medical record that a consultation was done by an allergist/immunologist, dermatologist or a rheumatologist regarding the diagnosis and treatment recommendations; and

e. The requested dose is:

1. Initial therapy: 150 mg every four weeks or 300 mg every four weeks and clinical rationale for starting therapy at 300 mg every four weeks has been provided.

2. Continuation of therapy: 150 mg or 300 mg every four weeks.

B. Nucala® (mepolizumab), Cinqair® (reslizumab)

1. All the following criteria must be met and documented:

a. The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies; and

b. The recipient must have a diagnosis of severe eosinophilic-phenotype asthma; and

c. The recipient must be an appropriate age:

1. Mepolizumab: 12 years of age or older

2. Reslizumab: 18 years of age or older

d. And, the prescriber must be either a pulmonologist or allergist/immunologist; and

e. The recipient must be uncontrolled on current therapy including high dose corticosteroid and/or on a secondary asthma inhaler; and

f. There is documentation of the recipient's vaccination status; and

g. The requested dose is appropriate:

1. Mepolizumab: 100 mg subcutaneously every four weeks.

2. Reslizumab: 3 mg/kg via intravenous infusion of 20 to 50 minutes every four weeks.

C. Fasenra® (benralizumab)

1. All the following criteria must be met and documented:

a. The recipient must be 12 years of age or older; and

b. The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthamtic monoclonal antibodies; and

c. The recipient must have a diagnosis of severe eosinophilic phenotype asthma; and

d. One of the following:

1. Patient has had at least two or more asthma exacerbations requiring systemic corticosteroids within the past 12 months; or

2. Any prior intubation for an asthma exacerbation; or

3. Prior asthma-related hospitalization within the past 12 months.

e. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

1. Both a high-dose inhaled corticosteroid (ICS) (e.g., greater than 500 mcg fluticasone propionate equivalent/day) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline); or

2. One maximally-dosed combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera

(mometasone/formoterol), Symbicort (budesonide/ formoterol)).

f. Prescribed by or in consultation with one of the following:

1. Pulmonologist; or

2. Allergy/Immunology specialist.

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

a. There is documentation of a positive clinical response (e.g., reduction in exacerbation).

b. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:

1. Both an inhaled corticosteroid (ICS) (5,E) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline); or

2. A combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/formoterol)).

c. Prescribed by or in consultation with one of the following:

1. Pulmonologist; or

2. Allergy/Immunology specialist.

2. Prior Authorization Guidelines

A. Prior authorization approval will be for 12 months.

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

Table 1: Dosing for Xolair® (omalizumab)*

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30-60	**>60-70**	**>70-90**	**>90-150**
≥30-100	150 mg	150 mg	150 mg	300 mg
>100-200	300 mg	300 mg	300 mg	225 mg
>200-300	300 mg	225 mg	225 mg	300 mg
>300-400	225 mg	225 mg	300 mg	
>400-500	300 mg	300 mg	375 mg	
>500-600	300 mg	375 mg		
>600-700	375 mg	**DO NOT DOSE**		
Every 2 Weeks Dosing				
Every 4 Weeks Dosing				

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*Centers for Disease Control and Prevention [CDC] 2019*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*CDC 2019*).
- The goal of asthma management – asthma control – can be described in the following domains (*National Heart, Lung, and Blood Institute [NHLBI] 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤ 2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (eg, omalizumab)
    - Leukotriene modulators
    - Long-acting beta-agonists (LABAs)
    - Methylxanthines (ie, theophylline)
  - Quick-relief medications include:
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent guideline from the Global Initiative for Asthma (GINA) on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level and allergic triggers to asthma (*GINA 2019b*)
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2019, Saini 2018*).

- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2018*).
- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2019, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Schwartz et al 2016).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus exacerbated by various environmental stimuli. It is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). A genetic defect that leads to dysfunction of the epidermal skin barrier along with an impaired immune response to microbial entry through the epidermis are believed to be the underlying causes of the condition (*Weston and Howe 2019a*).
- AD affects up to 25% of children and 2 to 3% of adults. It can manifest at different sites depending on the age at onset. The prevalence appears to be increasing especially in Western societies (*Sidbury et al 2014*, *Weston and Howe 2019a*).
- Topical emollients and topical corticosteroids are first-line treatments for AD. Topical calcineurin inhibitors are generally reserved as a second-line treatment option. The use of systemic therapies is reserved for patients with moderate to severe disease and can include phototherapy, oral cyclosporine, or other systemic immunosuppressants (*Weston and Howe 2019b*).
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma. Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in reduction of release of inflammatory mediators including cytokines, chemokines, nitric oxide and IgE. These actions are useful for eosinophilic asthma and controlling symptoms of moderate to severe AD.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Dupixent (dupilumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients 12 years of age and older with severe asthma with an eosinophilic phenotype			✔	✔	
Add-on maintenance treatment for patients 12 years of age and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients 18 years of age and older with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	
The treatment of adults and adolescents 12 years of age and older with CIU who remain symptomatic despite H_1-antihistamine treatment.					✔
Treatment of patients 12 years of age and older with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable		✔			

*None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
†Not indicated for treatment of other eosinophilic conditions
‡Not indicated for other allergic conditions or other forms of urticaria

(*Prescribing information: Cinqair 2019, Dupixent 2019, Fasenra 2017, Nucala 2019, Xolair 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

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).
- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60

weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).

- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; rate ratio, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.
- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

- Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit *(Ledford et al 2017)*.

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; $p < 0.0001$). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; $p = 0.096$). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/μL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; $p = 0.015$) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; $p = 0.049$) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (rate ratio, 0.55; 95% CI, 0.42 to 0.71; $p < 0.0001$) or every 8 weeks (rate ratio, 0.49; 95% CI, 0.37 to 0.64; $p < 0.0001$). Both doses of benralizumab also

significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (rate ratio, 0.64; 95% CI, 0.49 to 0.85; p = 0.0018) and every 8 weeks (rate ratio, 0.72; 95% CI, 0.54 to 0.95; p = 0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORO Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2018*).
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (p < 0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; p = 0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; p < 0.001).
- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; p < 0.0001). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; p < 0.0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; p < 0.00001) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that

benralizumab administration resulted no increasing incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; p = 0.96) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (p < 0.0001), 1.46 in the 250 mg mepolizumab group (p = 0.0005), and 1.15 in the 750 mg mepolizumab group (p < 0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (p < 0.001), and 0.83 per patient per year in the SC mepolizumab group (p < 0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (p < 0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; p = 0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (p = 0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio, 0.53; 95% CI, 0.44 to 0.62; p < 0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (rate ratio, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/μL to 70% (rate ratio, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/μL. At a baseline count < 150 cells/μL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were

respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).

- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (rate ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/μL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: rate ratio, 0.50; 95% CI, 0.37 to 0.67; Study 3083: rate ratio, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/μL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/μL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/μL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
  - An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients

initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) of patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).

- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; $p < 0.00001$). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; $p < 0.00001$). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; $p < 0.00001$). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).

DUPILUMAB

AD

- The efficacy and safety of dupilumab compared to placebo in adults with moderate-to-severe AD was evaluated in two Phase 3 trials, SOLO 1 (n = 671) and SOLO 2 (n = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to either placebo, dupilumab 300 mg SC weekly or every other week for 16 weeks. The proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear skin) and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome. In both studies between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo ($p < 0.001$ for all comparisons). Significantly more patients who received dupilumab had ≥ 75% improvement from baseline on the Eczema Area and Severity Index (EASI-75) compared to those who received placebo ($p < 0.001$). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common adverse effects with dupilumab compared to placebo were conjunctivitis and injection-site reactions (*Simpson et al 2016*).
- The long-term efficacy and safety of dupilumab was compared to placebo in 740 patients with moderate to severe AD not adequately controlled with topical corticosteroids in the LIBERTY AD CHRONOS study. Patients received either dupilumab 300 mg once weekly, once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were proportion of patients achieving an IGA score of 0 or 1 and ≥ 2 point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group ($p < 0.0001$). Similar efficacy results were reported at week 52. At 1 year, the most common adverse events associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab while herpes zoster and eczema herpeticum was more common in the placebo group (*Blauvelt et al 2017*).
- The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate-to-severe AD in a double-blind, multicenter, randomized controlled trial. Patients < 60 kg received dupilumab 400 mg initially then 200 mg every 2 weeks and patients ≥ 60 kg received 600 mg initially then 300 mg every 2 weeks for 16 weeks. The primary endpoint (proportion of patients achieving an IGA score of 0 or 1 and ≥ 2 point improvement from baseline to week 16) was achieved in 24% of dupilumab patients compared to 2% of placebo patients. EASI-75 was achieved by 42% of dupilumab and 8% of placebo patients (*Dupixent prescribing information 2019*).

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300/mm^3 was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo ($p < 0.0001$). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual

exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*).

- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).
- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR 0.44; 95% CI, 0.35 to 0.055; $p < 0.01$). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; $p < 0.01$). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR 1.91; 95% CI, 1.14 to 2.59; $p < 0.01$) (*Zayed et al 2018*).

COMPARATIVE REVIEWS

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated rate ratios of 0.66 (95% credible interval [CrI], 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CrI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median rate ratio of 0.63 (95% CrI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median rate ratio of 0.58 (95% CrI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more

previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019*).

- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/µL (rate ratio, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/µL (rate ratio, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/µL (rate ratio, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/µL (rate ratio, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/µL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/µL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/µL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/µL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/µL *(Busse et al 2019)*.
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018)*.
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score and AQLQ score. Event rates for asthma exacerbation and associated rate ratios were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2 tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. Increase in FEV_1, reduction in ACQ score and increase in AQLQ score was observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated rate ratio for annualized asthma exacerbation was significant only for dupilumab (rate ratio, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (rate ratio, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2019, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2019, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma was included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, 2 or more controllers or

taking maintenance oral corticosteroids), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis and nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high dose ICS/LABA or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency and patient preference. (*GINA 2019a, GINA 2019b*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab in patients with symptoms despite treatment with a 4-fold dose of modern second generation antihistamines. This is a change from previous guidelines in which use of either omalizumab or cyclosporine after failure of high-dose antihistamines was recommended. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should only be considered if omalizumab does not provide an adequate response. (*Zuberbier et al 2018*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Schwartz et al 2016*).
  - These guidelines have not been updated to include the place in therapy for mepolizumab; however, the EGPA Consensus Task Force recommendations notes that mepolizumab hold promise for this condition based on the pilot studies available at the time of guideline development (*Groh et al 2015*).

AD

- According to the American Academy of Dermatology, interventions that provide effective control of AD for a majority of patients include non-pharmacologic interventions with emollients, topical treatment with corticosteroids and calcineurin inhibitors, and avoidance of environmental triggers. Phototherapy is the next option for children and adults with moderate to severe AD not controlled with the first-line interventions. A third-line treatment recommended for patients who fail phototherapy is treatment with systemic immunomodulators, such as cyclosporine and methotrexate. The guidelines did not provide a recommendation on use of biologic agents due to limited data available at the time of publication (*Sidbury et al 2014*)
- 2017 guidance from the International Eczema Council provides clinicians with similar guidance as the American Academy of Dermatology as well as additional steps to be taken before initiation of systemic treatment. These include consideration of an alternative diagnosis, ensuring patient compliance with topical treatment, a trial of intensive topical therapy, treatment of infection, identification and avoidance of all potential triggers, and use of phototherapy if possible. The guidance does not comment on use of biologic agents due to limited data (*Simpson et al 2017*). The International Eczema Council also published a position statement on conjunctivitis in atopic dermatitis with and without dupilumab therapy based on an opinion survey and round table discussion of its members. Based on expert opinion, a consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior

to treatment, patients with new-onset conjunctivitis during dupilumab therapy should be referred to ophthalmologists, and treatment should be continued after referral to an ophthalmologist *(Thyssen et al 2019).*

- A 2018 European consensus guideline from a variety of organizations on treatment of atopic eczema includes dupilumab as a treatment option for patients with moderate-to-severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on use of pediatrics was provided due to lack of data. (*Wollenberg et al 2018*).

SAFETY SUMMARY

- All agents are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients in its formulation.
- Abrupt discontinuation of systemic, topical or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

Cinqair:

- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with Cinqair. If patients become infected while receiving Cinqair and do not respond to anti-helminth treatment, Cinqair should be discontinued until the parasitic infection resolves.
- The most common adverse reaction (≥ 2%) included oropharyngeal pain.

Dupixent:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with AD, conjunctivitis and keratitis has occurred more often when compared to placebo in clinical trials evaluating Dupixent. New or worsening eye symptoms should be reported to a healthcare provider.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- Most common adverse reactions in patients with AD included injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
- Most common adverse reactions in patients with asthma included injection site reactions, oropharyngeal pain, and eosinophilia.

Fasenra:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache and pharyngitis.

Nucala:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.
  - Herpes zoster infections have occurred in patients receiving Nucala. Vaccination should be considered if clinically appropriate.
  - Pre-existing helminth infections should be treated before therapy with Nucala. If patients become infected while receiving Nucala and do not respond to anti-helminth treatment, Nucala should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache, injection site reaction, back pain, and fatigue.

Xolair:

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Patients should be observed closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established.

Drug	Route	Usual Recommended Frequency	Comments
			• Cinqair should be administered by a healthcare professional.
Dupixent (dupilumab)	SC	AD: every other week Asthma: every other week	• AD and Asthma: Safety and efficacy in pediatric patients < 12 years of age have not been established. • Dupixent may be self-administered.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra should be administered by a healthcare professional.
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Safety and efficacy in pediatric patients other than those with asthma have not been established. • Nucala for injection (ie, powder for reconstitution) should be reconstituted and administered by a healthcare professional. • The Nucala auto injector and pre-filled safety syringe may be self-administered after the healthcare provider determines it is appropriate.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	• Xolair should be administered by a healthcare professional. Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight. • Safety and efficacy in pediatric patients with asthma < 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU < 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).

- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2019a, GINA 2019b, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA-approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, with demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy after confirmation of severe disease, along with individual patient factors (*GINA 2019a, GINA 2019b*).
- Dupixent is an IL-4/IL-13 antagonist with 2 FDA-approved indications: treatment of patients ≥ 12 years of age with moderate-to-severe AD, and treatment of patients ≥ 12 years of age with severe asthma of the eosinophilic type or dependent on oral corticosteroids. Its use in AD should be determined by its approved indication and clinician judgment. According to the most recent GINA guideline on treatment of severe asthma, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids.
- Nucala is the only IL-5 antagonist approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017).* A network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab. The only 2 agents that demonstrated a significant reduction in asthma exacerbation rates compared to placebo were reslizumab and dupilumab (*Iftikhar et al 2018*).
- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients ≥ 18 years of age (vs ≥ 12 years of age with Nucala and Fasenra), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 12 years of age with both severe asthma and AD.

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Publication Date: June 10, 2019

Prior Authorization Guideline

Guideline Name Nayzilam (midazolam)

1 . Indications

Drug Name: Nayzilam (midazolam) **Indications** **Seizures, acute intermittent:** benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

2 . Criteria

Product Name: Nayzilam

Diagnosis	Seizures, acute intermittent
Approval Length	6 Months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of acute intermittent seizures.

AND

2 Member is at least 12 years of age.

AND

3 The dose will not exceed two sprays per seizure cluster and no more than one episode every three days and treat no more than five episodes per month.

Product Name: Nayzilam

Diagnosis	Seizures, acute intermittent
Approval Length	12 Months
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

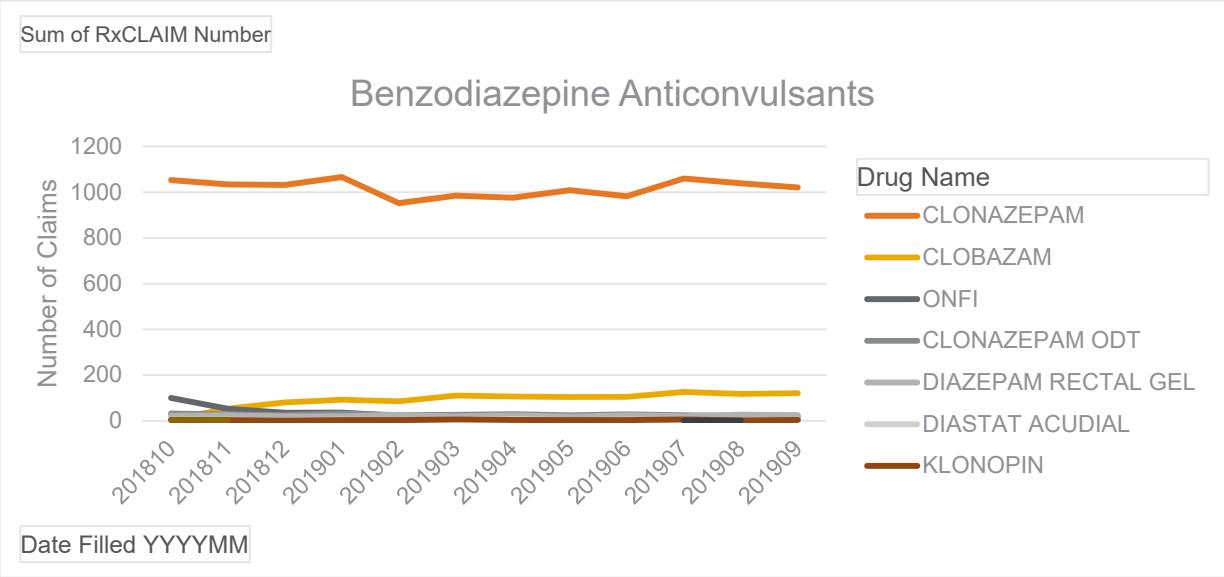
Approval Criteria

1 Documentation of positive clinical response to therapy (e.g., satisfactory response to acute treatment).

Nevada Medicaid

Benzodiazepine Anticonvulsants
Fee for Service
October 1, 2018 - September 30, 2019

Drug Name	Count of Members	Count of Claims	Days Supply	Total Qty
CLOBAZAM	158	1,105	32,978	162,706
CLONAZEPAM	2,209	12,209	331,032	667,359
CLONAZEPAM ODT	83	313	7,326	16,347
DIASTAT ACUDIAL	39	50	855	102
DIAZEPAM	7	7	45	13
DIAZEPAM RECTAL GEL	151	268	4,440	526
KLONOPIN	6	42	1,099	4,090
ONFI	113	327	9,719	49,433
SYMPAZAN	2	2	60	120



BBBB. Anticonvulsants

Therapeutic Class: Anticonvulsants
Last Reviewed by the DUR Board: January 24, 2019

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

Cannabinoid

Epidiolex® (cannabidiol)

1. Coverage and Limitations

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

   a. The recipient has a diagnosis of Lennox-Gastaut syndrome or Dravet Syndrome; and

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

   c. A recent serum transaminase (ALT and AST) and total bilirubin level has been obtained and is within normal limits; and

   d. The drug is prescribed by or in consultation with a neurologist; and

   e. The total dose does not exceed 20 mg/kg/day (10mg/kg twice daily); and

   f. The medication will be used as adjunctive therapy (the recipient has been taking one or more antiepileptic drugs and has chart notes confirming the presence of at least four convulsive seizures per month).

2. Recertification Request

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

   b. Serum transaminase (ALT and AST) and total bilirubin level has been re-checked per package insert.

3. Prior Authorization Guidelines

   a. Initial prior authorization will be for three 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

4. For anticonvulsant criteria for children and adolescents, refer to Section N, titled Psychotropic Medications for Children and Adolescents.

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium§)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔

Drug	Generic Availability
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid (Depacon, Depakene)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.
(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *			A		✔, A*	✔, A*		✔ *		✔, A*		A*	✔ *	✔, A*	A*
Primary generalized tonic-clonic seizure (grand mal)			✔								✔			✔ *			A*	A*
Absence seizure (petit mal)					✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures								A										
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *		A*	✔, A								A*				A*	
Seizures of Dravet syndrome		✔ *																
Juvenile myoclonic epilepsy (JME)																		A*
Emergency/acute/short-term use for seizure control (see notes)							✔ *							✔ *				
Akinetic and myoclonic seizures					✔, A													
Convulsive disorders (see notes)							A*											
Certain mixed seizure patterns or other partial or generalized seizures			✔ *															
Migraine prophylaxis								✔ *										
Trigeminal neuralgia			✔ *															
Postherpetic neuralgia															✔ *			
Bipolar disorder			✔ *					✔ *									✔ *	
Panic disorder, with or without agoraphobia					✔													
Anxiety disorder; short-term relief of anxiety symptoms						✔	✔											
Symptomatic relief of acute alcohol withdrawal						✔	✔											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome							A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)												A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓, A*		✓*		✓*	A*	✓, A*			A*	✓, A*	✓, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✓*		✓, A*				✓, A*			
Absence seizure (petit mal)		✓*												✓, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✓*			✓*			✓*									
Infantile spasms															✓*	
Convulsive disorders (see notes)						✓*										
Migraine prophylaxis													✓*	✓*		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- **Cannabidiol**:
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- **Carbamazepine**:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam**:
  - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam**:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam**:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)

- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age ≥ 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- **Eslicarbazepine**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- **Ethotoin**:
  - Complex partial (psychomotor) seizures
- **Everolimus:**
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- **Felbamate**:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin**:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin**:
  - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- **Lacosamide**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- **Lamotrigine immediate-release formulations**:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets**:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam**:
  - Adjunctive therapy in the treatment of partial onset seizures in adults and children ≥ 1 month of age with epilepsy (age ≥ 4 years and weighing > 20 kg for the tablets for oral suspension [Spritam])
  - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years with JME
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 12 years of age with epilepsy
- **Methsuximide**:

- Control of absence (petit mal) seizures that are refractory to other drugs
- **Midazolam nasal spray:**
  - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- **Oxcarbazepine immediate-release formulations**:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets**:
  - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- **Pentobarbital**:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel**:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved)**:
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations**:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection**:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin**:
  - Adjunctive therapy for treatment of partial onset seizures in patients ≥ 1 month of age
- **Primidone**:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide**:
  - Adults and pediatric patients ≥ 1 year of age
- **Stiripentol**:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- **Tiagabine**:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate**:
  - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- **Valproic acid**:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures

- **Vigabatrin**:
  - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
  - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide**:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

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

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
    - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
    - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
  - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
    - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.

        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
        - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.
- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically

significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.

- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannibidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al* 2018; *Devinsky et al* 2017). To date, no comparative trials have been published.
  - Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
  - In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*

- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following :
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
  - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations from the 2004 guideline include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.

        - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
        - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
        - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
        - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
    - Recommendations from the 2018 guideline include the following:
        - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
            - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
            - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
            - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
            - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
            - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
        - As monotherapy in patients with TRAFE:
            - Eslicarbazepine use may be considered to decrease seizure frequency.
            - Data are insufficient to recommend use of second- and the other third-generation AEDs.
        - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
        - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
        - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
            - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
            - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
            - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
            - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
        - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
    - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
    - Recommendations include the following:
        - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
        - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
        - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
        - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
        - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
    - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment

is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
    - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
    - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
  - Conclusions included the following (age not specified):
    - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
  - The overall treatment algorithm directs that:
    - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
    - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).

- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
  - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
  - Recommendations include the following:
    - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
    - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
    - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
    - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
    - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
    - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
  - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spams.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2016)
  - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
  - Recommendations include the following:
    - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
    - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
  - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
  - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate

- Dravet syndrome: topiramate, zonisamide, valproate
- Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
- Provoked or situational seizures: carbamazepine

▪ There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.

- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
    - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
    - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
    - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
    - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
    - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
    - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
    - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
    - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
    - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.

        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
    - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress).
    - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
    - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
    - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
        - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
        - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
        - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
        - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.

- Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2019*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:

- non-infectious pneumonitis
- infections
- hypersensitivity reactions
- angioedema (when taken with an angiotensin converting enzyme inhibitor)
- renal failure
- impaired wound healing
- myelosuppression
- reduced immune response with vaccination
- hyperglycemia
- hyperlipidemia
- embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	Oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (*Lexicomp 2019*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid (Depakene, Depacon)	capsules, oral solution/ syrup, injection	oral, IV	2 to 4 times per day (*Lexicomp 2019*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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Publication Date: September 30, 2019

Prior Authorization Guideline

Nevada Medicaid
Fee for Service

1 . Indications

Drug Name: Sunosi (solriamfetol)

Indications

Narcolepsy Indicated to improve wakefulness in adults patients with excessive daytime sleepiness associated with narcolepsy.

Obstructive sleep apnea (OSA) Indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with obstructive sleep apnea (OSA). Limitations of use: Sunosi is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating Sunosi for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with Sunosi. Sunosi is not a substitute for these modalities.

2 . Criteria

Product Name: Sunosi

Diagnosis	Narcolepsy
Approval Length	12 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1. Diagnosis of narcolepsy as confirmed by sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible)

AND

2. Trial and failure, contraindication or intolerance to both of the following:
    a. modafinil

b. armodafinil

Product Name: Sunosi

Diagnosis	Narcolepsy
Approval Length	12 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Documentation of positive clinical response to Sunosi therapy.

Product Name: Sunosi

Diagnosis	Obstructive Sleep Apnea (OSA)
Approval Length	6 Month
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 Diagnosis of obstructive sleep apnea defined by one of the following:

a. 15 or more obstructive respiratory events per hour of sleep confirmed by a sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible)

OR

b. Both of the following:
   i. 5 or more obstructive respiratory events per hour of sleep confirmed by a sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible)
   ii. One of the following signs/symptoms are present:
      1. Daytime sleepiness
      2. Nonrestorative sleep
      3. Fatigue
      4. Insomnia
      5. Waking up with breath holding, gasping, or choking
      6. Habitual snoring noted by a bed partner or other observer

7. Observed apnea

AND

2 Both of the following:
   a. Standard treatment(s) for the underlying obstruction (e.g., with continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP]) have been used for one month or longer
   b. Patient is fully compliant with ongoing treatment(s) for the underlying airway obstruction

AND

3 Trial and failure, contraindication or intolerance to both of the following:
   a. modafinil
   b. armodafinil

Product Name: Sunosi

Diagnosis	Obstructive Sleep Apnea (OSA)
Approval Length	6 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 Documentation of positive clinical response to Sunosi therapy.

AND

2 Patient continues to be fully compliant with ongoing treatment(s) for the underlying airway obstruction (e.g., CPAP, BiPAP)

3 . Endnotes

A. International Classification of Sleep Disorders (ICSD-3) diagnostic criteria for narcolepsy type 1 (narcolepsy with cataplexy) require: 1) Daily periods of irrepressible need to sleep or daytime lapses into sleep (i.e., excessive daytime sleepiness) occurring for at least 3 months. 2) The presence of one or both of the following: cataplexy and a mean sleep

latency of less than or equal to 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT; or cerebrospinal fluid (CSF) hypocretin-1 concentration is low (less than or equal to 110 pg/mL or less than one-third of mean values obtained in normal subjects with the same standardized assay) [2,3].

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

C. Examples of obstructive respiratory events include: obstructive and mixed apneas, hypopneas, or respiratory effort related arousals (RERA) [2].

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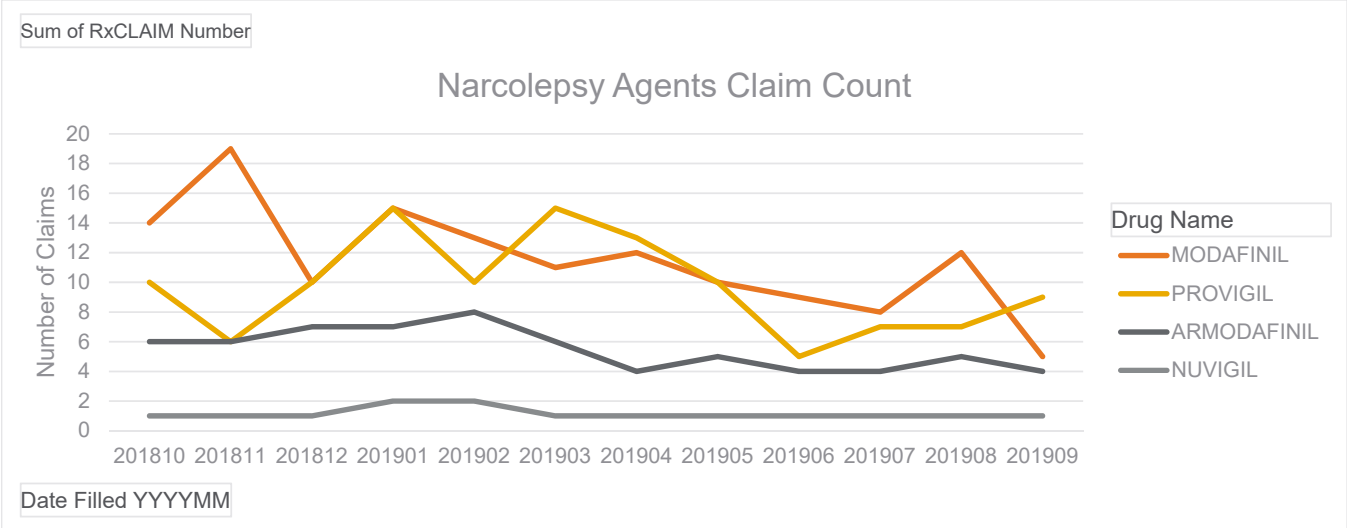
Nevada Medicaid

Narcolepsy Agents
Fee for Service
October 1, 2018 - September 30, 2019

Drug Name	Count of Members	Count of Claims	Days Supply	Total Qty
ARMODAFINIL	11	66	1981	1981
MODAFINIL	28	138	3675	4170
NUVIGIL	1	14	370	740
PROVIGIL	25	117	2563	2833



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

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

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

1. Coverage and Limitations

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

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

      1. The recipient has a diagnosis of narcolepsy.

   b. Xyrem® (sodium oxybate):

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

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

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

2. Prior Authorization Guidelines

   a. Prior authorization approvals will be for one year.

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

INTRODUCTION

- Narcolepsy is a lifelong neurological sleep disorder of hypersomnia characterized by excessive daytime sleepiness (EDS) and intermittent manifestations of rapid eye movement (REM) sleep during wakefulness. Excessive sleepiness is defined by the International Classification of Sleep Disorders, third edition (ICSD-3) as "daily episodes of an irrepressible need to sleep or daytime lapses into sleep" (*Sateia 2014*).
- Patients with narcolepsy often have many nighttime arousals and sleep disturbances that contribute to excessive drowsiness during the day. EDS can vary in severity, and some patients involuntarily fall asleep during normal daily activities. This can put the patient or others at risk if these daytime lapses into sleep occur during activities such as operating a motor vehicle. While all patients with narcolepsy experience EDS, additional symptoms may include cataplexy, which is the sudden and complete loss of muscle tone, dream-like images or hallucinations at sleep onset or awakening, and sleep paralysis (*National Institute of Neurological Disorders and Stroke [NINDS] 2017, Scammell 2019).*
- The ICSD-3 establishes 2 subtypes of narcolepsy: narcolepsy type 1 and narcolepsy type 2. Patients are diagnosed with narcolepsy type 1 if they have 1 or both of the following: (1) a cerebrospinal fluid (CSF) hypocretin-1 deficiency; (2) clear cataplexy and a mean sleep latency of < 8 minutes on the multiple sleep latency test (MSLT) with evidence of 2 sleep-onset rapid-eye movement periods (SOREMPs), one of which may be seen on a preceding overnight polysomnogram. A diagnosis of narcolepsy type 2 also requires a mean sleep latency of < 8 minutes on the MSLT and at least 2 SOREMPs, but cataplexy must be absent and CSF hypocretin-1 levels must not meet the type 1 criterion *(Sateia 2014).*
- Narcolepsy affects males and females equally. While symptoms typically begin to present in the teens or early twenties, they can occur at any time throughout a patients' life (*NINDS 2017, Scammell 2019*). It is estimated that approximately 135,000 to 200,000 people in the United States (US) are diagnosed with narcolepsy; however, this number may actually be higher as many patients often go undiagnosed (*NINDS 2017).* Narcolepsy is a chronic condition, but does not typically get worse over time. There is no cure for narcolepsy but there are pharmacological and nonpharmacological options that can be implemented to help patients manage their symptoms. The goal of therapy is to mitigate symptoms in order to improve the patient's quality of life (*Morgenthaler et al 2007a, NINDS 2017*).
- This review will focus on 2 wakefulness promoting agents, modafinil (Provigil) and armodafinil (Nuvigil), 1 central nervous system (CNS) depressant agent, sodium oxybate (Xyrem), and 1 dopamine norepinephrine reuptake inhibitor (DNRI), solriamfetol (Sunosi). These 4 medications are approved by the US Food and Drug Administration (FDA) for the symptomatic treatment of narcolepsy. There are several amphetamine-like stimulant medications indicated for the treatment of narcolepsy; however, they will not be covered in this review.
- Modafinil and armodafinil (the longer half-life R-enantiomer of modafinil) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), and shift work disorder (SWD). OSA is a sleep disorder that is characterized by obstructive apneas and hypopneas, causing patients to have frequent sleep interruptions due to increased respiratory effort. Often, patients do not feel rested in the morning and continue to have excessive sleepiness throughout the day (*American Academy of Sleep Medicine [AASM] 2009, Strohl 2019*). SWD is a circadian rhythm sleep disorder that occurs in individuals who work non-traditional hours and is characterized by excessive sleepiness and/or insomnia (*Morgenthaler et al 2007b*). Modafinil and armodafinil have been shown to produce psychoactive and euphoric effects similar to CNS stimulants, as well as alterations in mood, perception, thinking and feelings. As a result, these agents are classified as Schedule IV controlled substances.
- Sodium oxybate is gamma-hydroxybutyric acid (GHB), a known drug of abuse. It is FDA-approved for the treatment of EDS and cataplexy in patients ≥ 7 years of age with narcolepsy and is classified as a Schedule III controlled substance for these indications. However, non-medical uses of sodium oxybate are classified under Schedule I. Sodium oxybate carries a boxed warning regarding CNS depression, abuse, and misuse, and may only be dispensed to patients enrolled in the Xyrem Risk Evaluation and Mitigation Strategy (REMS) program using a specially certified pharmacy. Prescribers and patients must also be enrolled in this REMS program (*Xyrem REMS Web site).*
- Solriamfetol is FDA-approved to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA. Solriamfetol is pending U.S. Controlled Substances Act scheduling (*Sunosi dossier 2019*).

- While placebo-controlled (PC) clinical studies document the efficacy of these agents, the exact mechanisms of action are not completely understood. Head-to-head studies are limited, and current clinical guidelines recommend modafinil and sodium oxybate as first-line treatments for EDS and cataplexy, respectively.
- Medispan class: Stimulants – misc.; Anti-cataplectic agents.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Nuvigil (armodafinil)	✔
Provigil (modafinil)	✔
Sunosi (solriamfetol)	-
Xyrem (sodium oxybate)	-

(*Drugs@FDA 2019, Orange Book: approved drug products with therapeutic equivalence evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Nuvigil (armodafinil)	Provigil (modafinil)	Sunosi (solriamfetol)	Xyrem (sodium oxybate)
To improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD	✔	✔		
To improve wakefulness in adult patients with EDS associated with narcolepsy or OSA			✔	
For the treatment of cataplexy and EDS in narcolepsy in patients ≥ 7 years of age				✔

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

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

CLINICAL EFFICACY SUMMARY

Narcolepsy

- The efficacy of modafinil for EDS associated with narcolepsy was established in 2 multicenter (MC), double-blind (DB), PC, randomized controlled trials (RCTs). In both studies, patients treated with modafinil showed statistically significant improvement in objective measures of excessive sleepiness as measured by the MSLT and Maintenance of Wakefulness Test (MWT); and the subjective Epworth Sleepiness Scale (ESS) compared to placebo ($p < 0.001$ for all endpoints in both studies). Overall clinical condition as rated by the Clinical Global Impression of Change (CGI-C) at the final visit was also significantly improved over baseline for patients treated with modafinil compared to placebo in both studies ($p < 0.005$ and $p < 0.03$) (*US Modafinil in Narcolepsy Multicenter Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000).*
- The efficacy of armodafinil for EDS associated with narcolepsy was established in a MC, DB, PC, RCT. Patients treated with armodafinil showed a statistically significant enhanced ability to remain awake as measured by the MWT compared to placebo ($p < 0.01$), as well as improvement in overall clinical condition as rated by the CGI-C compared to placebo ($p < 0.0001$). Armodafinil was also associated with statistically significant improvements in memory, attention, and fatigue ($p < 0.05$) (*Harsh et al 2006).*
- The effectiveness of sodium oxybate in the treatment of EDS in patients with narcolepsy was established in 2 MC, DB, PC, RCTs.

- In the first study, patients treated with sodium oxybate 6 and 9 grams per night achieved statistically significant improvements on the ESS, MWT, and CGI-C compared to the placebo group ($p < 0.001$ for all) (*Xyrem International Study Group 2005a*).
- The second study required patients to be taking a stable dose of modafinil before study randomization. Patients were randomized to placebo, sodium oxybate, modafinil, or sodium oxybate plus modafinil. Patients who were switched from modafinil to sodium oxybate did not experience any decrease in sleep latency, suggesting that both medications are equally effective for EDS. Patients taking sodium oxybate alone and sodium oxybate plus modafinil had statistically significant improvements in sleep latency from baseline as measured by MWT compared to the placebo group ($p < 0.001$). The sodium oxybate plus modafinil group showed a significantly greater increase in sleep latency from baseline compared to the sodium oxybate alone group ($p < 0.001$), suggesting that the combination of drugs had an additive effect (*Black & Houghton 2006*).

- The efficacy of sodium oxybate in the treatment of cataplexy in patients with narcolepsy was established in 2 DB, PC, RCTs.
  - In the first study, patients treated with 6 and 9 grams per night saw a significant decrease in cataplexy attacks compared to placebo ($p < 0.05$ for both doses) (*U.S. Xyrem Multicenter Study Group 2002*).
  - The second study was a randomized withdrawal trial including narcoleptic patients already established on sodium oxybate therapy prior to study entry. Patients were randomized to continue treatment with sodium oxybate or to placebo, which included discontinuation of sodium oxybate therapy. Patients who discontinued sodium oxybate experienced a significant increase in cataplexy attacks compared to patients who remained on sodium oxybate ($p < 0.001$) (*U.S. Xyrem Multicenter Study Group 2004*).
- The efficacy of solriamfetol for the treatment of narcolepsy or narcolepsy with cataplexy was evaluated in a DB, PC, MC, RCT (*Thorpy et al 2019*). Patients were stratified on the basis of presence or absence of cataplexy. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups. At week 12, treatment with solriamfetol significantly improved mean sleep latency measured by the MWT vs placebo ($p < 0.0001$) and ESS scores ($p \leq 0.02$). Significantly higher percentages of patients treated with solriamfetol also reported improvements in Patient Global Impression of Change (PGI-C) vs placebo ($p < 0.0001$). There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).

OSA

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

- An OL extension study evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Sunosi dossier 2019*). In

a 2-week OL titration phase, patients received solriamfetol, titrated to a maximum tolerated dose, followed by a maintenance phase. During a 2-week PC randomized withdrawal phase ~6 months later, patients were randomized either to placebo or to continue their maintenance solriamfetol dose for 2 weeks. From the beginning to the end of the randomized withdrawal phase, the ESS score was significantly improved with solriamfetol vs placebo ($p < 0.0001$). The percentage of patients who were reported as worse on the PGI-C at the end of the randomized withdrawal phase was greater for patients randomized to placebo compared to patients on solriamfetol ($p < 0.0001$). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores. During the randomized withdrawal period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

SWD

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

- Armodafinil, modafinil, sodium oxybate, and solriamfetol have all been shown to be more effective compared to placebo for their respective FDA-approved indications, as demonstrated by significant improvements in objective and subjective measures of EDS. In addition, sodium oxybate has been shown to significantly reduce the rate of cataplexy attacks in narcolepsy patients compared to placebo. While there is insufficient evidence to suggest that one agent is more efficacious than another, some studies have demonstrated that concurrent therapy with sodium oxybate and modafinil had a greater effect on EDS and wakefulness than either agent on its own, suggesting an additive effect (*Alshaikh et al 2012, Billiard et al 1994, Black & Houghton 2006, Black et al 2010a, Black et al 2010b, Black et al 2016, Broughton et al 1997, Kuan et al 2016, Xyrem International Study Group 2005b, Schwartz et al 2010, Weaver et al 2006).*

CLINICAL GUIDELINES

Narcolepsy:

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

OSA:

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

SWD:

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

SAFETY SUMMARY

- Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency and when used in combination with sedative hypnotics or alcohol.
- Sodium oxybate carries a boxed warning regarding CNS depression and misuse and abuse.
  - Respiratory depression may occur; the concurrent use of sodium oxybate with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - As a sodium salt of the Schedule I controlled substance GHB, sodium oxybate abuse or misuse may be associated with CNS AEs including seizure, respiratory depression, decreased levels of consciousness, coma, and death.
  - Because of these risks, sodium oxybate is only available through a restricted distribution program called the Xyrem REMS program using a central pharmacy that is specially certified. Prescribers and patients must also enroll in the program (*Xyrem REMS Web site*).
- Additional warnings and precautions for sodium oxybate include:
  - Patients should avoid participation in hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that sodium oxybate does not adversely affect them.
  - Monitor patients for signs of new or increased depression and suicidality, impaired motor and cognitive function, and episodes of sleepwalking.
  - Due to its high sodium content, patients with heart failure, hypertension, or impaired renal function should be routinely monitored while taking sodium oxybate.
- Common AEs with sodium oxybate were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

- Warnings and Precautions for modafinil and armodafinil include:
  - Cases of serious rash, including Stevens-Johnson Syndrome, have been reported. Discontinue therapy at the first sign of rash unless certain rash is not drug-related.
  - Angioedema and anaphylaxis reactions may occur. Discontinue therapy and immediately seek medical attention at the first signs of angioedema or anaphylaxis.
  - Multi-organ hypersensitivity reactions may occur. There are no known factors to predict the risk of occurrence or the severity of the reaction, and therapy should be discontinued in these patients.
  - Persistent sleepiness: patients should be regularly assessed for degree of sleepiness and advised against driving or other potentially dangerous activities if necessary.
  - The emergence or exacerbation of psychiatric symptoms have been reported; use particular caution in patients with a history of psychosis, depression, or mania.
  - Consider increased monitoring in patients with known cardiovascular disease.

- The most common AEs with modafinil were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia; the most common AEs with armodafinil were headache, nausea, dizziness, and insomnia.
- Drug interactions for modafinil and armodafinil:
  - Exposure to CYP 3A4/5 substrates may be decreased:
    - Effectiveness of steroidal contraceptives may be reduced; use alternative or concomitant contraceptive methods while taking and for 1 month after discontinuation of modafinil or armodafinil.
    - Blood concentrations of cyclosporine may be reduced requiring monitoring and possible dose adjustment.
  - Exposure to CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam, may be increased.
  - More frequent monitoring of prothrombin times/international normalized ratio (INR) should be considered when administered with warfarin.
  - Use caution when concomitantly used with monoamine oxidase inhibitors (MAOIs).

- Solriamfetol is contraindicated with concomitant use of MAOIs, or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
- Warnings and precautions of solriamfetol include blood pressure and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
- The most common AEs in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, insomnia, and anxiety.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

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

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

See the current prescribing information for full details

CONCLUSION

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

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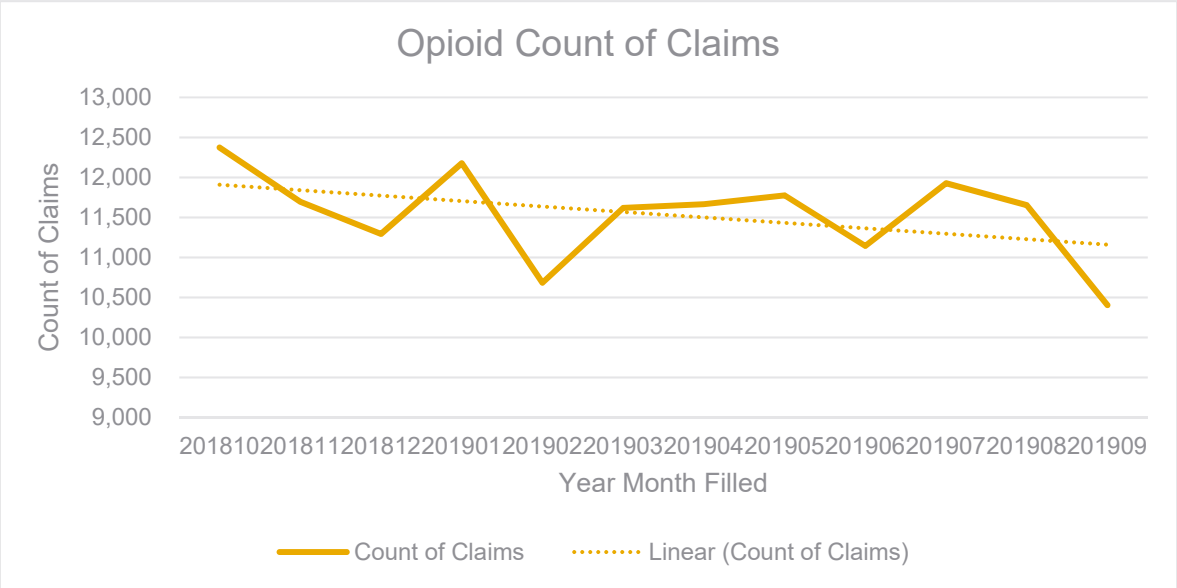
Board Requested Reports

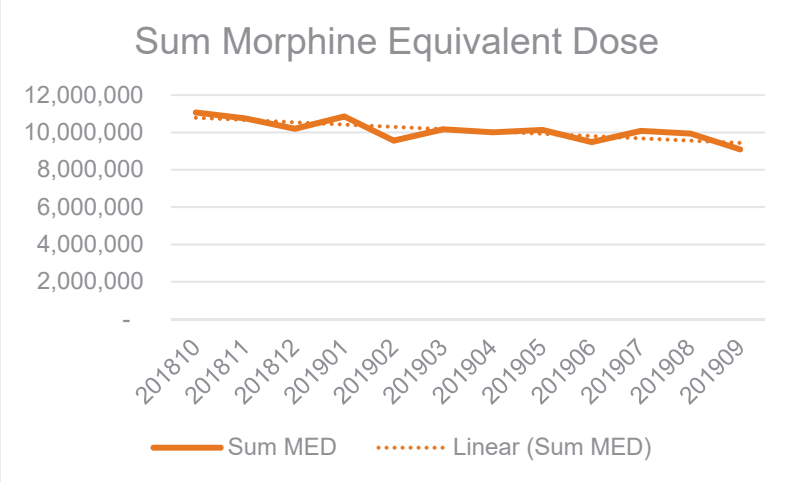
Nevada Medicaid

Opioid Utilization Summary
Fee for Service
October 1, 2018 - September 30, 2019

Date Filled	Count of Mer	Count of Claims	Total Days Supply	Total Quantity
201810	8,469	12,374	224,132	767,175
201811	8,215	11,696	216,258	740,566
201812	7,957	11,293	206,884	700,426
201901	8,523	12,178	221,404	746,727
201902	7,772	10,684	197,231	658,884
201903	8,158	11,619	209,738	695,374
201904	8,156	11,666	209,616	697,792
201905	8,059	11,775	211,711	711,798
201906	7,903	11,143	198,803	656,350
201907	8,202	11,927	212,273	699,694
201908	8,081	11,653	211,795	693,516
201909	7,638	10,405	195,683	637,704



Date Filled	Sum MED
201810	11,071,052
201811	10,753,602
201812	10,194,764
201901	10,857,862
201902	9,565,700
201903	10,170,065
201904	10,009,443
201905	10,133,323
201906	9,484,068
201907	10,084,818
201908	9,942,251
201909	9,090,705



Opioid Utilization by Prescriber - Top 10

Fee for Service Medicaid

Quarter 2, 2019 and Quarter 3, 2019

Quarter 3, 2019

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

Quarter 2, 2019

Prescriber	Specialty	City	Count of Member	Count of Claims	Days Supply	Total Qty	Sum of MED
A	MD - Anesthesiolgist	Reno	203	475	13,685	57,376	830,646
E	PA - No Specialty	Las Vegas	120	286	8,327	27,099	645,685
C	PA - Pain Management	Las Vegas	110	286	8,460	31,779	595,863
K	APRN - Neurology	Las Vegas	104	207	5,657	19,700	492,570
L	APRN - No Specialty	Las Vegas	228	394	11,080	37,084	484,004
M	APRN - Acute Care	Las Vegas	105	219	5,766	19,655	387,455
N	MD - OB/GYN	Henderson	44	87	2,615	10,408	372,140
O	PA - No Specialty	Las Vegas	107	163	4,113	13,792	344,148
H	PA - No Specialty	Las Vegas	98	180	5,199	19,522	333,707
J	PA - Pain Management	Las Vegas	95	179	5,115	22,920	323,563

Opioid Utilization by Member - Top 10

Fee for Service Medicaid

Quarter 3, 2019

Member ID Encrypted	Count of Claims	Days Supply	Total Qty	Sum of MED	
71367188889	8	240	840	57,600	
33330458115	6	180	1,080	57,600	
11110100737	11	318	1,780	55,200	
99990949361	9	212	987	53,955	*Prescriber A
66667788323	10	300	1,080	49,950	
33338530549	13	217	545	47,820	
44448546720	6	180	1,260	47,250	
44446597311	5	150	570	45,900	
10687255556	6	180	660	45,600	
49044066667	6	168	924	45,360	

Member ID Encrypted	Drug Name	MED Value per Unit	Count of Claims	Days Supply	Total Qty	Sum of MED
10687255556	HYDROMORPHONE HCL TAB 8 MG	32.00	3	90	300	9,600
10687255556	MORPHINE SULF TAB CR 100 MG	100.00	3	90	360	36,000
11110100737	METHADONE HCL TAB 10 MG		3	84	820	
11110100737	MORPHINE SULF TAB CR 100 MG	100.00	4	114	480	48,000
11110100737	OXYCODONE HCL TAB 10 MG	15.00	4	120	480	7,200
33330458115	MORPHINE SULF TAB CR 100 MG	100.00	3	90	360	36,000
33330458115	OXYCODONE HCL TAB 20 MG	30.00	3	90	720	21,600
33338530549	FENTANYL TD PAT 72H 100MCG/HR	720.00	5	93	61	43,920
33338530549	HYDROCODONE-APAP TAB 10-325 MG	10.00	1	30	120	1,200
33338530549	HYDROCODONE-APAP TAB 7.5-325MG	7.50	3	90	360	2,700
33338530549	HYDROMORPHONE HCL INJ 1 MG/ML	0.00	3	3	3	-
33338530549	HYDROMORPHONE HCL INJ 2 MG/ML	0.00	1	1	1	-
44446597311	FENTANYL TD PAT 72H 100MCG/HR	720.00	2	60	30	21,600
44446597311	OXYCODONE HCL TAB 30 MG	45.00	3	90	540	24,300
44448546720	HYDROCODONE-APAP TAB 10-325 MG	10.00	3	90	270	2,700
44448546720	OXYCODONE HCL TAB 30 MG	45.00	3	90	990	44,550
49044066667	MORPHINE SULF TAB CR 60 MG	60.00	3	84	252	15,120

49044066667	OXYCODONE HCL TAB 30 MG	45.00	3	84	672	30,240
66667788323	MORPHINE SULF TAB CR 30 MG	30.00	3	90	270	8,100
66667788323	MORPHINE SULF TAB CR 60 MG	60.00	4	120	360	21,600
66667788323	OXYCODONE HCL TAB 30 MG	45.00	3	90	450	20,250
71367188889	MORPHINE SULF TAB CR 100 MG	100.00	4	120	360	36,000
71367188889	OXYCODONE HCL TAB 30 MG	45.00	4	120	480	21,600
99990949361	OXYCODONE HCL TAB 30 MG	45.00	5	106	775	34,875
99990949361	OXYMORPH HCL TAB SR12HR 30MG	90.00	4	106	212	19,080

Opioid and Benzo Utilization - Top 10

Fee for Service Medicaid

Quarter 3, 2019

Top 10 opioid utilizing members and related benzos

Member ID Encrypted	Prescriber ID	Drug Label Name	Count of Claims	Total Days Supply	Total Quantity
10687255556					
11110100737	GG	ALPRAZOLAM TAB 1 MG	4	120	480
33330458115	BB	DIAZEPAM TAB 10 MG	3	90	90
33338530549	CC	ALPRAZOLAM TAB 0.5 MG	3	90	180
33338530549	FF	LORAZEPAM INJ 2 MG/ML	1	1	1
44446597311	GG	DIAZEPAM TAB 10 MG	3	90	270
44448546720	GG	ALPRAZOLAM TAB 0.5 MG	3	75	135
49044066667					
66667788323	DD	ALPRAZOLAM TAB 2 MG	2	60	180
66667788323	DD	ALPRAZOLAM TAB 1 MG	2	60	180
71367188889	EE	ALPRAZOLAM TAB 2 MG	4	120	265
99990949361	AA	DIAZEPAM TAB 10 MG	3	90	360

Top 10 Opioid Prescribers and related benzos

Prescriber	Count of Members	Drug Label Name	Count of Claims	Total Days Supply	Total Quantity
A	1	HYDROXYZ HCL TAB 10MG	3	90	180
B	7	ALPRAZOLAM TAB 0.5MG	10	214	546
B	5	BUSPIRONE TAB 10MG	8	139	343
B	15	ALPRAZOLAM TAB 1MG	22	467	1,235
B	1	HYDROXYZ HCL TAB 25MG	1	14	42
B	2	LORAZEPAM TAB 2MG	3	75	180
B	3	LORAZEPAM TAB 1MG	4	89	208
B	4	ALPRAZOLAM TAB 0.25MG	8	178	282
B	1	DIAZEPAM TAB 2MG	1	30	60
B	5	HYDROXYZ PAM CAP 50MG	9	153	545
B	2	DIAZEPAM TAB 5MG	2	60	90
B	4	HYDROXYZ HCL TAB 50MG	6	180	330
B	2	LORAZEPAM TAB 0.5MG	2	37	134
B	9	ALPRAZOLAM TAB 2MG	16	416	924
B	15	BUSPIRONE TAB 15MG	23	558	1,480
B	5	DIAZEPAM TAB 10MG	10	300	600
B	3	BUSPIRONE TAB 30MG	3	90	210
B	9	HYDROXYZ PAM CAP 25MG	9	169	538
C	3	HYDROXYZ HCL TAB 25MG	3	90	180
C	2	HYDROXYZ HCL TAB 50MG	3	90	120
C	2	DIAZEPAM TAB 10MG	4	120	150
C	1	ALPRAZOLAM TAB 1MG	3	90	270
D	1	DIAZEPAM TAB 10MG	1	30	20
D	3	DIAZEPAM TAB 5MG	6	180	255
D	1	HYDROXYZ HCL TAB 10MG	1	30	60
E					
F	1	BUSPIRONE TAB 10MG	2	60	180
F	1	LORAZEPAM TAB 2MG	3	90	270
G	2	HYDROXYZ HCL TAB 25MG	2	60	90
H	1	DIAZEPAM TAB 10MG	2	60	75
I	1	BUSPIRONE TAB 10MG	1	30	30
I	1	DIAZEPAM TAB 5MG	2	60	60
I	2	ALPRAZOLAM TAB 1MG	5	150	150
I	2	BUSPIRONE TAB 15MG	3	90	180
I	2	DIAZEPAM TAB 10MG	3	90	90
I	2	HYDROXYZ HCL TAB 25MG	2	60	180
I	1	ALPRAZOLAM TAB 0.5MG	2	60	60
I	2	HYDROXYZ HCL TAB 50MG	3	90	150
I	2	ALPRAZOLAM TAB 0.25MG	5	150	390
J					

Standard DUR Reports

Nevada Medicaid

Top 10 Therapeutic Classes

Fee for Service

Quarter 2, 2019 and Quarter 3, 2019

Top 10 Drug Classes by Paid Amount - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTIHEMOPHILIC PRODUCTS**	105	$ 13,934,712.96
ANTIRETROVIRALS**	1,715	$ 3,630,727.10
INSULIN**	4,575	$ 3,292,745.13
SYMPATHOMIMETICS**	17,998	$ 2,687,726.44
ANTICONVULSANTS - MISC.**	26,243	$ 2,663,767.99
BENZISOXAZOLES**	5,657	$ 2,391,336.02
ANTIPSYCHOTICS - MISC.**	2,791	$ 2,180,498.89
QUINOLINONE DERIVATIVES**	4,823	$ 1,763,706.31
ANTINEOPLASTIC ENZYME INHIBITORS**	155	$ 1,762,464.98
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES**	263	$ 1,583,220.23

Top 10 Drug Classes by Paid Amount - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTIHEMOPHILIC PRODUCTS**	120	$ 13,815,305.37
ANTIRETROVIRALS**	1,770	$ 3,623,775.23
INSULIN**	4,511	$ 3,219,888.78
ANTICONVULSANTS - MISC.**	26,228	$ 3,136,088.28
SYMPATHOMIMETICS**	18,621	$ 2,813,507.12
BENZISOXAZOLES**	5,694	$ 2,368,461.24
ANTIPSYCHOTICS - MISC.**	2,683	$ 1,991,217.40
QUINOLINONE DERIVATIVES**	4,671	$ 1,724,732.75
HEPATITIS AGENTS**	123	$ 1,619,065.20
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES**	257	$ 1,608,538.28

Top 10 Drug Classes by Claim Count - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,243	$ 2,663,767.99
SYMPATHOMIMETICS**	17,998	$ 2,687,726.44
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,924	$ 207,348.08
OPIOID COMBINATIONS**	15,212	$ 440,104.10
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,258	$ 347,639.13
CENTRAL MUSCLE RELAXANTS**	12,546	$ 223,260.79
HMG COA REDUCTASE INHIBITORS**	10,443	$ 338,186.76
OPIOID AGONISTS**	10,093	$ 640,428.53
DIBENZAPINES**	9,647	$ 378,359.54
BENZODIAZEPINES**	8,322	$ 103,377.86

Top 10 Drug Classes by Claim Count - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid Amt
ANTICONVULSANTS - MISC.**	26,228	$ 3,136,088.28
SYMPATHOMIMETICS**	18,621	$ 2,813,507.12
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,786	$ 208,720.88
OPIOID COMBINATIONS**	15,465	$ 454,813.24
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,195	$ 297,990.22
CENTRAL MUSCLE RELAXANTS**	12,288	$ 221,846.93
HMG COA REDUCTASE INHIBITORS**	10,616	$ 329,588.19
OPIOID AGONISTS**	10,227	$ 638,553.27
DIBENZAPINES**	9,490	$ 354,313.49
BENZODIAZEPINES**	8,514	$ 107,392.14

RxTrack®

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

From 7/1/19 Through 9/30/19

Dec 9, 2019
10:19:35 AM

Claims Summary:

RxCLAIM Status	Total Rxs with cDUR(s)	% Total Rxs with cDUR(s)	Total Rxs with No cDURs	% Total Rxs with No cDURs	Total Rxs	% Total Rxs	Total Plan Paid	Total Member Paid
Paid	259,523	72.41%	283,269	59.35%	542,792	64.95%	$52,416,717.54	$0.00
Rejected	63,410	17.69%	155,089	32.49%	218,499	26.15%		
Reversed	35,466	9.90%	38,919	8.15%	74,385	8.90%		
Totals	**358,399**	**100.00%**	**477,277**	**100.00%**	**835,676**	**100.00%**		

cDUR Information Summary Table:

	Total cDURs			cDURs on Paid Rxs			cDURs on Rejected Rxs			cDURs on Reversed Rxs		
cDUR Type	Total cDUR Triggered Events	Count	% of All cDURs	Count	% of cDUR Type	% Total cDURs	Count	% of cDUR Type	% Total cDURs	Count	% of cDUR Type	% Total cDURs
Dosing/Duration (DOSECHEK)	69,486	48,257	13.46%	42,339	87.74%	16.31%	308	0.64%	0.49%	5,610	11.63%	15.82%
Drug-Drug Interaction (DDI-DTMS)	466,714	146,176	40.79%	127,004	86.88%	48.94%	5,397	3.69%	8.51%	13,775	9.42%	38.84%
Drug Age Caution (DRUG_AGE)	14	14	0.00%	12	85.71%	0.00%	0	0.0%	0.0%	2	14.29%	0.01%
Duplicate Rx (DUPRX)	69,787	66,967	18.69%	16,850	25.16%	6.49%	45,071	67.30%	71.08%	5,046	7.54%	14.23%
Duplicate Therapy (DUPTHER)	143,627	58,332	16.28%	40,022	68.61%	15.42%	12,634	21.66%	19.92%	5,676	9.73%	16.00%
Drug Regimen Compliance (COMPLIAN)	41,946	38,653	10.78%	33,296	86.14%	12.83%	0	0.0%	0.0%	5,357	13.86%	15.10%
Total All cDURs	**791,574**	**358,399**	**100.00%**	**259,523**	**72.41%**	**100.00%**	**63,410**	**17.69%**	**100.00%**	**35,466**	**9.90%**	**100.00%**

RXT6050D - Summarized DUR Activity Report

From 7/1/19 Through 9/30/19

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

DUR Service	Top Drug Drug Interaction	GPI 4	GPI 4 Description	GPI 4/ Therapy / Reason	GPI 04 Description	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per RX	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount	Top PPS CODE USED #1	Top PPS CODE USED #2	Top PPS CODE USED #3
Dosing/Duration (DOSECHEK)	CYCLOBENZAPRINE HYDROCHLORIDE	7510	NA	MAX DAYS THERAPY = 21	CENTRAL MUSCLE RELAXANTS**	Message	2,458	$28,829.72	$9.44	$0.00	32.4	68.4	0	191	$2,002.97			
Dosing/Duration (DOSECHEK)	ONDANSETRON ODT	5025	NA	GERIATRIC MIN DLY = 2.00UN	5-HT3 RECEPTOR ANTAGONISTS**	Message	954	$420.61	$0.35	$0.00	1.5	1.4	0	51	$33.13			
Dosing/Duration (DOSECHEK)	FAMOTIDINE	4920	NA	GERIATRIC MIN DLY = 4.00UN	H-2 ANTAGONISTS**	Message	688	$671.10	$0.81	$0.00	1.0	2.0	0	27	$24.58			
Dosing/Duration (DOSECHEK)	HEPARIN SODIUM	8310	NA	GERIATRIC MIN DLY = 4.00UN	HEPARINS AND HEPARINOID-LIKE AGENTS**	Message	659	$2,284.92	$2.23	$0.00	1.1	1.7	0	26	$159.87			
Dosing/Duration (DOSECHEK)	CETIRIZINE HYDROCHLORIDE	4155	NA	GERIATRIC MAX DLY = .50UN	ANTIHISTAMINES - NON-SEDATING**	Message	592	$6,886.16	$10.40	$0.00	39.0	39.0	0	44	$453.08			
Dosing/Duration (DOSECHEK)	ATORVASTATIN CALCIUM	3940	NA	MIN. DAYS THERAPY = 7	HMG COA REDUCTASE INHIBITORS**	Message	541	$174.18	$0.22	$0.00	1.0	1.3	0	64	$12.36			
Dosing/Duration (DOSECHEK)	KETOROLAC TROMETHAMINE	6610	NA	GERIATRIC MAX DLY = 2.00UN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Message	537	$6,585.68	$7.99	$0.00	1.0	5.8	0	28	$158.89			
Dosing/Duration (DOSECHEK)	POTASSIUM CHLORIDE ER	7970	NA	ADULT MIN DLY = 2.00 UN	POTASSIUM**	Message	480	$9,334.75	$15.89	$0.00	43.3	42.7	0	62	$1,011.86			
Dosing/Duration (DOSECHEK)	LISINOPRIL	3610	NA	MIN. DAYS THERAPY = 7	ACE INHIBITORS**	Message	419	$80.88	$0.12	$0.00	1.0	1.4	0	56	$18.30			
Dosing/Duration (DOSECHEK)	PANTOPRAZOLE SODIUM	4927	NA	MIN. DAYS THERAPY = 7	PROTON PUMP INHIBITORS**	Message	393	$113.43	$0.23	$0.00	1.1	1.1	0	50	$3.54			
Drug Age Caution (DRUG_AGE)	NITROFURANTOIN	5300	NA	AGE LESS THAN 4	URINARY ANTI-INFECTIVES**	Message	4	$1,465.49	$366.37	$0.00	22.5	167.5	0	0				
Drug Age Caution (DRUG_AGE)	ACETAMINOPHEN/CODEINE	6599	NA	AGE LESS THAN 10	OPIOID COMBINATIONS**	Message	2	$29.64	$8.57	$0.00	7.5	107.5	0	2	$12.50			
Drug Age Caution (DRUG_AGE)	PROMETHAZINE HCL PLAIN	4140	NA	AGE LESS THAN 4	ANTIHISTAMINES - PHENOTHIAZINES**	Message	2	$20.26	$10.13	$0.00	8.0	120.0	0	0				
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/DEXTROMETHORPHAN	4399	NA	AGE LESS THAN 4	COUGH/COLD/ALLERGY COMBINATIONS**	Message	2	$23.22	$11.61	$0.00	11.0	70.0	0	0				
Drug Age Caution (DRUG_AGE)	PROMETHAZINE HCL	4140	NA	AGE LESS THAN 4	ANTIHISTAMINES - PHENOTHIAZINES**	Message	1	$67.76	$67.76	$0.00	3.0	12.0	0	0				
Drug Age Caution (DRUG_AGE)	COMPOUND CLAIM	0000	NA	ING01 AGE LESS THAN 4	-	Message	1	$15.33	$15.33	$0.00	30.0	80.0	0	0				
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7260	NA	7 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	51	$881.61	$13.64	$0.00	30.0	90.9	0	9	$144.18			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	9 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	47	$5,477.54	$93.21	$0.00	22.7	7.3	0	9	$1,009.86			
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7260	NA	8 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	46	$677.66	$12.81	$0.00	29.0	96.8	0	6	$88.40			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	7 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	42	$5,338.54	$88.37	$0.00	24.6	7.2	0	17	$1,626.94			
Drug Regimen Compliance (COMPLIAN)	MONTELUKAST SODIUM	4450	NA	7 DAYS LATE REFILLING	LEUKOTRIENE MODULATORS**	Message	42	$702.60	$13.66	$0.00	30.0	30.0	0	11	$103.40			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	8 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	39	$5,064.40	$92.59	$0.00	21.0	7.2	0	15	$1,453.54			
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7260	NA	11 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	39	$509.13	$12.47	$0.00	29.0	95.7	0	1	$21.61			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	11 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	37	$4,777.56	$98.94	$0.00	21.8	8.0	0	11	$1,030.22			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	13 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	37	$4,187.22	$94.97	$0.00	22.1	7.4	0	5	$586.54			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	10 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	33	$4,211.38	$88.83	$0.00	21.8	7.1	0	13	$1,280.14			
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	4420	NA	12 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	28	$3,697.56	$94.90	$0.00	20.4	7.4	0	12	$1,040.40			
Drug-Drug Interaction (DDI-DTMS)	ATORVASTATIN CALCIUM	3940	NA	CLOPIDOGREL TAB 75MG	HMG COA REDUCTASE INHIBITORS**	Message	859	$12,574.58	$10.42	$0.00	50.8	51.0	0	105	$1,165.67			
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	5710	NA	HYDROCO/APAP TAB 10-325MG	BENZODIAZEPINES**	Message	620	$7,486.99	$9.96	$0.00	28.1	59.4	0	30	$301.62			
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	5710	NA	OXYCOD/APAP TAB 10-325MG	BENZODIAZEPINES**	Message	404	$4,974.11	$10.08	$0.00	27.8	62.5	0	16	$179.50			
Drug-Drug Interaction (DDI-DTMS)	HYDROCODONE/ACETAMINOPHEN	6599	NA	ALPRAZOLAM TAB 1MG	OPIOID COMBINATIONS**	Message	375	$7,176.84	$14.60	$0.00	24.4	83.8	0	18	$382.12			
Drug-Drug Interaction (DDI-DTMS)	METFORMIN HYDROCHLORIDE	2725	NA	LISINOPRIL TAB 20MG	BIGUANIDES**	Message	367	$3,970.27	$8.15	$0.00	62.9	127.6	0	40	$287.70			
Drug-Drug Interaction (DDI-DTMS)	AMLODIPINE BESYLATE	3400	NA	CLOPIDOGREL TAB 75MG	CALCIUM CHANNEL BLOCKERS**	Message	353	$3,036.58	$5.68	$0.00	60.5	63.7	0	44	$297.59			
Drug-Drug Interaction (DDI-DTMS)	ONDANSETRON HYDROCHLORIDE	5025	NA	HYDROCO/APAP TAB 10-325MG	5-HT3 RECEPTOR ANTAGONISTS**	Message	352	$2,850.45	$6.07	$0.00	3.5	9.6	0	17	$153.87			
Drug-Drug Interaction (DDI-DTMS)	GABAPENTIN	7260	NA	MORPHINE SUL TAB 15MG ER	ANTICONVULSANTS - MISC.**	Message	332	$6,005.67	$14.03	$0.00	30.0	92.0	0	18	$335.38			
Drug-Drug Interaction (DDI-DTMS)	ONDANSETRON HYDROCHLORIDE	5025	NA	HYDROCO/APAP TAB 5-325MG	5-HT3 RECEPTOR ANTAGONISTS**	Message	298	$846.83	$2.17	$0.00	1.5	4.1	0	23	$30.78			
Drug-Drug Interaction (DDI-DTMS)	LISINOPRIL	3610	NA	METFORMIN TAB 500MG	ACE INHIBITORS**	Message	290	$5,709.80	$7.29	$0.00	67.1	73.9	0	37	$600.24			
Duplicate Rx (DUPRX)	HYDROCODONE/ACETAMINOPHEN	6599	NA	HYDROCO/APAP TAB 10-325MG	OPIOID COMBINATIONS**	Hard Reject	6	$5,361.56	$22.10	$0.00	30.0	112.5	280	2	$44.34			
Duplicate Rx (DUPRX)	GABAPENTIN	7260	NA	GABAPENTIN CAP 300MG	ANTICONVULSANTS - MISC.**	Soft Reject	2	$5,387.25	$14.16	$0.00	30.0	75.0	391	0				
Duplicate Rx (DUPRX)	EPOGEN	8240	NA	EPOGEN INJ 10000/ML	HEMATOPOIETIC GROWTH FACTORS**	Soft Reject	0	$51,819.44					1,346	0				
Duplicate Rx (DUPRX)	SODIUM CHLORIDE	7975	NA	SOD CHLORIDE INJ 0.9%	SODIUM**	Soft Reject	0	$2,019.02					926	0				
Duplicate Rx (DUPRX)	ONDANSETRON HYDROCHLORIDE	5025	NA	ONDANSETRON INJ 4MG/2ML	5-HT3 RECEPTOR ANTAGONISTS**	Soft Reject	0	$225.31					418	0				
Duplicate Rx (DUPRX)	HECTOROL	3090	NA	HECTOROL INJ 4MCG/2ML	METABOLIC MODIFIERS**	Soft Reject	0	$1,724.25					414	0				
Duplicate Rx (DUPRX)	ATORVASTATIN CALCIUM	3940	NA	ATORVASTATIN TAB 40MG	HMG COA REDUCTASE INHIBITORS**	Soft Reject	0	$3,096.57					351	0				
Duplicate Rx (DUPRX)	PANTOPRAZOLE SODIUM	4927	NA	PANTOPRAZOLE TAB 40MG	PROTON PUMP INHIBITORS**	Soft Reject	0	$2,256.67					321	0				
Duplicate Rx (DUPRX)	MORPHINE SULFATE	6510	NA	MORPHINE SUL INJ 4MG/ML	OPIOID AGONISTS**	Soft Reject	0	$1,305.84					306	0				
Duplicate Rx (DUPRX)	AMLODIPINE BESYLATE	3400	NA	AMLODIPINE TAB 10MG	CALCIUM CHANNEL BLOCKERS**	Soft Reject	0	$2,463.73					289	0				
Duplicate Therapy (DUPTHER)	MORPHINE SULFATE	6510	NA	SHORT ACTING NARCOTIC ANALGESI	OPIOID AGONISTS**	Message	867	$4,385.73	$3.21	$0.00	1.0	1.7	0	65	$207.03			
Duplicate Therapy (DUPTHER)	KETOROLAC TROMETHAMINE	6610	NA	NON-STEROIDAL ANTI-INFLAMMATOR	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Message	708	$3,862.46	$4.58	$0.00	1.0	2.3	0	18	$53.22			
Duplicate Therapy (DUPTHER)	QUETIAPINE FUMARATE	5915	NA	ORAL ANTIPSYCHOTICS	DIBENZAPINES**	Extract	526	$12,900.52	$12.73	$0.00	31.7	41.4	0	43	$1,326.50	TD,M0,1G		
Duplicate Therapy (DUPTHER)	RISPERIDONE	5907	NA	ORAL ANTIPSYCHOTICS	BENZISOXAZOLES**	Extract	347	$7,315.34	$11.32	$0.00	30.8	49.7	0	32	$816.71	TD,M0,1G		
Duplicate Therapy (DUPTHER)	GABAPENTIN	7260	NA	GABAPENTIN AND RELATED	ANTICONVULSANTS - MISC.**	Extract	322	$9,916.22	$14.47	$0.00	35.7	108.2	0	57	$2,222.54	TD,M0,1G		
Duplicate Therapy (DUPTHER)	HYDROCODONE/ACETAMINOPHEN	6599	NA	SHORT ACTING NARCOTIC ANALGESI	OPIOID COMBINATIONS**	Message	310	$89.00	$0.15	$0.00	1.0	1.6	0	46	$8.40			
Duplicate Therapy (DUPTHER)	DEXAMETHASONE SODIUM PHOSPHATE	2210	NA	GLUCOCORTICOSTEROIDS	GLUCOCORTICOSTEROIDS**	Message	266	$3,308.30	$7.75	$0.00	1.0	6.3	0	11	$27.70			
Duplicate Therapy (DUPTHER)	LEVOTHYROXINE SODIUM	2810	NA	THYROID HORMONES	THYROID HORMONES**	Extract	236	$7,068.61	$17.40	$0.00	56.0	54.5	0	52	$1,337.40	TD,M0,1G		
Duplicate Therapy (DUPTHER)	HYDROMORPHONE HCL	6510	NA	SHORT ACTING NARCOTIC ANALGESI	OPIOID AGONISTS**	Message	232	$1,052.18	$3.14	$0.00	1.0	1.5	0	26	$98.13			
Duplicate Therapy (DUPTHER)	GABAPENTIN	7260	NA	GABAPENTIN AND RELATED	ANTICONVULSANTS - MISC.**	Soft Reject	0	$18,795.58					257	0				
Total							**16,246**	**$291,514.03**	**$1,431.32**	**$0.00**	**1,052.5**	**2,169.047**	**5,299**	**1,410**	**$22,152.75**			

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

Nevada Medicaid

Retro-DUR Activities

Fee for Service

Quarter 3, 2019

Month	Clinical Initiative	Profiles Reviewed	Members Identified	Letters Sent	Responses
July 2019	Diabetes without Statin	>1000	61	73	4
August 2019	Two or more long-acting opioids	1155	0	0	0
August 2019	Albuterol without Long-term control	>1000	90	90	3
September 2019	High Dose ADHD Medications	2729	9	0	0

August 2019 -

During the time period of June 2019 to August 2019, there were 1155 members receiving long acting opioids.
Of the 1155 profiles reviewed, there were 213 members that received only 1 long acting opioid claim. 942 members received 2 or more long acting opioid claims.
Of the 942 members receiving 2 or more long acting opioids, there were 11 members that switched from one long acting opioid to another.
There were no members receiving more than one long acting opioid at the same time.

September 2019 -

During the time period of June 2019 to August 2019, there were 2729 members that received an ADHD medication.
Of the 2729 profiles reviewed, there were 9 members that received doses that were higher than the recommended dose.