

Nevada Medicaid Drug Use Review Board Meeting

October 17, 2019



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting: September 13, 2019
Date of Revision: September 17, 2019

Date of Meeting: 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 Ln
Reno, NV 89502
Phone: (775) 826-2500

Webinar Registration: <https://optum.webex.com/optum/onstage/g.php?MTID=e78d290166063056ec16813fcca8f0461>

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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 July 25, 2019
 - b. Status Update by the DHCFP
 1. Proclamation by Governor Sisolak in recognition of International Overdose Awareness Day.
 2. ~~Impact of AB-474 report.~~ Statistics related to opioid prescriptions rates, number of potential “doctor shoppers,” number of Prescription Monitoring Program (PMP) queries and number of individuals co-prescribed benzodiazepines and opioids.
 3. DHCFP policy updates.
4. **Clinical Presentations**
 - a. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Zolgensma (onasemnogene abeparvovec-xioi)
 1. Public comment on proposed clinical prior authorization criteria.
 2. Presentation of utilization and clinical information.
 3. Discussion by Board and review of utilization data.
 4. Proposed adoption of updated prior authorization criteria.
 - b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for 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.
 - c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for hematopoietic/hematinic 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 Regranex (becaplermin)
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 topical, local anesthetics
1. Public comment on proposed clinical prior authorization criteria.
 2. Presentation of utilization and clinical information.
 3. Discussion by Board and review of utilization data.
 4. Proposed adoption of updated prior authorization criteria.
- f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for inhaled anticholinergic 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.
- g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Daliresp (roflumilast)
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.
- h. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical antiparasitics
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.
- i. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for topical immunomodulators
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.

- j. **For Possible Action:** Presentation, discussion and possible adoption of updated DUR Bylaws
 - 1. Presentation by the DHCFP of updates to DUR Bylaws
 - 2. Discussion by Board and review of updates to DUR Bylaws
 - 3. Proposed adoption of updated DUR Bylaws.

5. 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.
- c. Lock-in program
 - 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.
- d. Naloxone utilization in members receiving opioids
 - 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.
- e. Aranesp (darbepoetin alfa) utilization
 - 1. Discussion by the Board and review of utilization data.
 - 2. **For Possible Action:** Requests for further evaluation or proposed clinical criteria to be presented at a later date.
- f. Antibiotic (third generation cephalosporins, fluoroquinolones and oxazolidinones) utilization
 - 1. Discussion by the Board and review of utilization data.
 - 2. **For Possible Action:** Requests for further evaluation or proposed clinical criteria to be presented at a later date.

6. Standard DUR Reports

- a. Review of Prescribing/Program Trends.

1. Top 10 Therapeutic Classes for first quarter 2019 and second quarter 2019 (by Payment and by Claims).
- b. Concurrent Drug Utilization Review (ProDUR)
 1. Review of second quarter 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.

7. 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, Reno District Office, Elko District 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

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:

Paul Oesterman, Pharm D, Chair

Brian Le, DO

Netochi Adeolokun, Pharm.D.

James Marx, MD

Mark Canty, MD

Michael Owens, MD

Dave England, Pharm D

Jim Tran, Pharm.D.

Mohammad Khan, MD

Jennifer Wheeler, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2019

Date	Time	Location
October 17, 2019	1:00 PM	Hyatt Place, Reno, NV

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/dhcfpnv.gov/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





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DRUG USE REVIEW BOARD

MEETING MINUTES

Date of Meeting: Thursday, July 25, 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 Ln
Reno, NV 89502
Phone: (775) 826-2500

ATTENDEES

Board Members Present

Paul Oesterman, Pharm.D., Chair
Netochi Adeolodun, Pharm.D.
Mark Canty, MD
Dave England, Pharm.D.
Brian Le, DO
James Marx, MD
Jim Tran, Pharm.D.
Jennifer Wheeler, Pharm.D.

Board Members Absent

Mohammad Khan, MD
Michael Owens, MD

DHCFP

Holly Long, Social Services Program Specialist
Beth Slamowitz, Pharm.D.
Julie Slabaugh, Deputy Attorney General

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

Antonio Guidino-Vargas

Stephanie Yamamoto, Janssen

Robin Reedy, NAMI NV

Suzanne Hensley, Xeris

Jimmy Lau, Ferrari Public Affairs

Amy Rodenburg, Allergan

Heather Lunsford, Carrara Nevada

Lea Cartwright, NPA

Doug Burlani, Sobi

Karen Meier, Novo Nordisk

Melissa Sommers, Novartis

Ann Nelson, Vertex

Public Online:

Mike Willden, The Perkins Company

Jeana Colabianchi, Sunovian

AGENDA

1. Call to Order and Roll Call

Called to order at 1:00 PM

Paul Oesterman, Chair: Welcome to the Nevada Medicaid Drug Use Review Board.

Roll call:

Jim Tran, Pharm.D.

Mark Canty, MD

Dave England, Pharm.D.

James Marx, MD

Brian Le, DO

Netochi Adeolokun, Pharm.D.

Jennifer Wheeler, Pharm.D.

Paul Oesterman, Pharm.D., Chair

Julie Slabaugh, DAG

Carl Jeffery

Holly Long

Beth Slamowitz

Ryan Bitton

Tom Beranek

Lisa Todd

2. Public Comment on Any Matter on the Agenda

Paul Oesterman, Chair: We do have a quorum so we will proceed. Is there any public comment?

Robin Reedy: I am Robin Reedy, Executive Director of the Nation Alliance on Mental Illness, Nevada. NAMI NV is a grassroots organization representing individuals living with mental illness and the families and friends that love them. We are dedicated to improving the lives of all those affected by mental illness, including making sure that individuals simultaneously combatting co-occurring disorders, receiving effective and efficient treatment. Accordingly, NAMI NV strongly supports limiting the duration of a step-therapy (also known as “fail first”) imposed by regulators, legislators, or insurers. Our primary goal in this policy arena is to allow a prescriber of a covered prescription drug or device to have prompt access to a process to override the step therapy or pre-authorization especially for antipsychotics and antidepressants. Clinical judgment and patient choice must always take precedence about individual care and decisions related to patient care must always rest with the patient’s physician or health care practitioner. We would like to give practitioners the ability to override the step-therapy protocol under specific circumstances and establish guidelines for an expeditious process when it is in the best interest of the patient. Limit the time period a patient can be subjected to step therapy for a period no longer than 30 days. We hope that, as you review classes of drugs, you will strongly consider refining “fail first”, preauthorization requirements and other barriers on antipsychotics and anti-depressants. Thank you for your time and consideration, as well as for your service to Nevada.

3. Administrative

Paul Oesterman, Chair: Does anyone from the Board have questions? Just FYI, we do have some people on the phone, if they have any comments, please speak up. Hearing none, we will move to the administrative portion. We need a motion and second to approve the minutes.

Motion made to accept the minutes as presented, seconded. Voting: Ayes across the Board with one abstention, the motion carries.

Paul Oesterman, Chair: We will now ask for an update from the DHCFP.

Holly Long: My name is Holly Long with DHCFP Pharmacy Services. The first thing I wanted to do is introduce the new Board members. We are excited to have these amazing new members. Dr. Brian Le, he has a doctor of osteopathic medicine from the New York College of Osteopathic Medicine. He is currently the medical director and an interventional pain specialist at the Las Vegas Pain and Spine Center in Las Vegas. He has an impressive list of professional experiences and awards. Dr. Mark Canty, currently practicing in geriatric private practice. He was previously the medical director of Silver Summit Health Plan. He brings experience as a physician lead in acute private practice for geriatrics, post-acute hospitalist for Renown, private practice family medicine, program development and as a mentor for post-acute in Central Illinois where he was providing direct patient care for approximately 500 nursing home patients.

Pharmacist Jim Tran, currently the director of pharmacy for Desert Springs Hospital Medical Center bringing expertise in cardiology, policy review and development and health systems implementation. Dr. Tran is the chair of the Medication Safety Committee as well as a member of various health care committees. Lastly, we have Dr. Mohammad Khan who could not be here today. He is Board Certified as a forensic psychiatrist and is currently the associate medical director for forensic services at Stein Forensics Hospital in Las Vegas. He is the senior psychiatrist for Southern Nevada Adult Mental Health Services and a clinical professor at UNR School of Medicine. Dr. Khan brings experience as a psychiatrist unit chief, staff psychiatry and clinical instructor throughout Nevada, New York and Wisconsin. As well as a number of publications and presentations in the field of psychiatry. I would also like to provide an update regarding overdose deaths. I know that this has been a topic of interest previously. I wanted to let everyone know that there have been two recent articles published where the CDC provided information stating that for the first time since 1990 the number of overdose deaths is starting to fall instead of climb. So, hopefully we can update everyone with Nevada specific data in the future. The other update I would like to provide is in relation to Senate Bill 378. It does not affect the DUR Board specifically but does affect what was the P&T Committee. I will go through a high-level overview of the provisions. I encourage everyone to visit the NELIS site to review the bill if you have further questions. The P&T Committee has been removed and all of its members. That provision was effective June 30, 2019. The Committee has been replaced and renamed to Silver State Scripts Board. The Board has the same responsibilities as the P&T Committee. It will continue to establish and maintain the PDL. The Silver State Scripts Board members are no longer appointed by the Governor as of June 30 and going forward, they will all be appointed by the Director of DHHS. The Board is now allowed to have a closed-door discussion on cost of drugs and drug-classes when clinical efficacy, safety and outcomes for two or more drugs is established. This Bill also allows the governing body or agency of the State of Nevada that provides coverage of prescription drugs to use the PDL as its formulary. That is all I have for today. I will add that we will be going over the DUR Bylaws at the end. The public is welcome to leave when we get to that agenda topic.

4. Clinical Presentations

- a. **For Possible Action:** Discussion and Possible Adoption of Updated Prior Authorization Criteria and/or Quantity Limits for Growth Hormones.

Paul Oesterman, Chair: Thank you. We will move to our clinical presentations. Our first item for possible action is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for growth hormones. Do we have any public comment? Hearing none, we will go ahead and get the presentation of the clinical information.

Carl Jeffery: In your binder, you have the updated criteria for growth hormone. This has not been reviewed for quite some time. We thought it would be good for the Board to review and make any changes necessary. We get some feedback from the endocrinologist community about some problems here and there, but nothing specific. We do several hearing preparation meeting where we meet with physicians that prescribe this. They give us feedback at that time and that has prompted us to review these criteria today. I updated the criteria to reflect our commercial criteria. I highlighted in red the changes I propose. It gets more specific for ages, it lists bone age and growth percentile. It breaks out the specific diagnosis and the different criteria.

James Marx: Are there any of the different products excluded or are we strictly using the indications to determine which product is approved? The summary shows a slew of different drugs with different indications. Does our process account for the differences?

Carl Jeffery: Each medication would have to have the indication. It does still apply to the FDA approved indication. They are all the somatostatin, it is the delivery device that is different and the studies they have done to get it approved by the FDA.

Paul Oesterman, Chair: I see the three managed care organization have reviewed it. Lisa, I see you had some comments, have they been incorporated?

Lisa Todd: I don't see they have. There were a few medications I do not see listed. There are some newer name brand drugs.

Paul Oesterman, Chair: I know in the past we have had classes of drugs like this, we try to keep the drug names out as possible.

Carl Jeffery: Yes, we -try to exclude the specific drugs names. This reduces the requirements to review again when a new drug is added in the marketplace.

Lisa Todd: I think my question was about the brand names in the criteria. I didn't know if that is something that we need to include. I think one of the things to point out was one of the indications was the SHOX gene. It is mentioned in the indications, but I did not see it in the criteria.

Carl Jeffery: I am not familiar with the SHOX gene. We removed idiopathic short stature from a covered benefit the last time we reviewed this class. I don't know if the SHOX gene is related to idiopathic short stature.

Beth Slamowitz: For clarification, all the drug names and indications would need to be appropriate for the approval to take place. The only addition in red below, which would be simply attestations from the providers that the lab values or clinical information is present.

Carl Jeffery: That is right. If the Board approves the criteria, I don't think the brand names need to be put in Chapter 1200. I include that information for the Board's reference.

Paul Oesterman, Chair: We do have some utilization data. Not a whole lot of use. It seems to be consistent with what I see in the real world. We need to get a motion and a second for the proposed growth hormone criteria.

Motion to accept the criteria as presented. Seconded.

James Marx: On the adult growth hormone deficiency, where they have a permanent issue like pan-hypopituitarism. They have to get renewed every 12 months? That is not an indication that will ever improve.

Carl Jeffery: We don't have any other criteria go beyond a year for approval. Even if the criteria is to check in to make sure the provider is still seeing that member. If we put a PA in forever, there is a concern there may be a lack of follow-up.

James Marx: There will be a lot of follow up necessary for those with pan-hypopituitarism.

Beth Slamowitz: I think from a process, it is just normal process to not extend PA authorization beyond 12 months.

Paul Oesterman, Chair: Any further discussion?

Voting: Ayes across the Board, the motion carries.

- b. **For Possible Action:** Discussion and Possible Adoption of Prior Authorization Criteria and/or Quantity Limits for Spravato® (esketamine).

Paul Oesterman, Chair: Our second clinical presentation for possible action is the discussion and possible adoption of prior authorization criteria and/or quantity limits for Spravato or esketamine. Is there any public comment?

Stephanie Yamamoto: Good afternoon, my name is Stephanie Yamamoto. I am a clinical pharmacist and director for value and evidence or basically health economics at Janssen Pharmaceuticals. I will speaking on behalf of Spravato today. Regarding the suggested criteria of failure of augmentation and the suggested criteria of failure of antidepressants in different classes for more than two antidepressants, we ask that you consider the landmark STAR-D data. That data did show a response of admission rates with marked decreased with after non-response to two antidepressant treatments. Remission rates were 30.6% and 36.8% at steps one and two vs. 13% and 13.7% at steps three and four. So, this emphasizes the importance of using more effective treatments earlier to optimize treatment outcomes for patients. The STAR-D data also indicates that there are no significant differences in switching within the class or to different classes of antidepressants. Consideration would be to amend the criteria to allow Spravato once adequate trials of dose and duration of two antidepressants have been exhausted. Thank you so much for your time and considerations.

Paul Oesterman, Chair: Thank you. We also have a letter that was received from Dr. Leslie Dixon who is a State Representative of the Nevada Psychiatric Association. We have second person present, go ahead.

Robin Reedy: Robin Reedy with NAMI NV. I think it is pretty apparent that we want broader distribution of something like this to help our members. We have the utmost respect for the Psychiatric Association and the work they do. But we also need to recognize that we are number 51 in the State for mental health services. Anything we can do to remove barriers to help people with mental health conditions.

Paul Oesterman, Chair: I appreciate your input with how the State ranks in terms of psychiatric patients. We also tend to rank high in the number of prescription per patient. So we also rank in the top five in that category. I think we need to meld the two so we need to make sure the appropriate medications are prescribed to the appropriate patients.

Robin Reedy: Yes, I agree with you. No one bit fits everyone. So, when you see a lot of prescriptions for patients, they are trying to find a fit. Sometimes you get the wrong med first, it takes a while to get the others.

Paul Oesterman, Chair: Thank you.

Carl Jeffery: The proposed criteria starts on page 71 in your binder. This is a new medication. I think Stephanie gave a brief summary of what this is for. It is a nasal spray of esketamine indicated for treatment resistant depression. It is scheduled and limited distribution pharmacies. It is pretty locked down. It needs to be administered in the doctor's office once a week. It is not an easy medication to administer and still requires a lot of follow-up. The criteria states the patient has a diagnosis of treatment resistant depression. I didn't include any kind of specific failure of two other agents before, by definition, that is treatment resistant depression. The other

thing I reconsidered after I put the criteria together is the last bullet point. Prescribed by a psychiatrist, I think the Board could consider making that prescribed by or in consultation with a psychiatrist. We have a lot of rural Nevadans that don't always have access to a psychiatrist. Once they are seen by a psychiatrist and it is determined they need to be on this, they can go to family practice for administration.

James Marx: Does this form differ from the racemic ketamine used for sedation?

Brian Le: I agree with you to add in conjunction with consultation with a psychiatrist. But it has to be administered by the physician. If it is not administered and monitored correctly, it can have a lot of problems.

James Marx: I agree. I have given hundreds of doses of ketamine over the years. The response is very variable. They actually have medics in the service use it now. But it is a very serious drug to be handed out. There can be some very serious reaction. Does the manufacture have any data on that?

Stephanie Yamamoto: You were asking about the side effects? I will note that the REMS program does require a two-hour monitoring after each administration. The most typical side effects include dissociation and increased blood pressure. That is what the REMS program is designed to monitor. It also includes sedation as well as nausea.

James Marx: How does it differ from ketamine used in anesthesia?

Stephanie Yamamoto: It is the S-enantiomer.

Brian Le: How much dissociation did you observe after administration?

Stephanie Yamamoto: Per the phase three trials, it was dissociation and up to 40%. The monitoring occurred it would peak around 40 minutes and go on up to two hours.

James Marx: What treatment was required for those hallucinations?

Stephanie Yamamoto: There was no treatment required. However, they did recommend the patients should stay in a quieter room to be able to be monitored. The requirement for the REMS program is the patients are not supposed to be driving until a good night's rest.

Carl Jeffery: Based on Dr. Le's input, would the board want to add criteria that it must be administered under the supervision of a prescriber's office? With the REMS, there is not a need for the criteria, but a safeguard.

James Marx: I think somewhere in the criteria something should be added about monitoring with some provision of the treatment of adverse events that might occur. I think just saying you have to have a doctor around isn't going to be enough.

Beth Slamowitz: The REMS program requires the monitoring.

James Marx: But REMS programs are so poorly administered.

Beth Slamowitz: But we do not have any further oversight than the REMS program. You can put it in the criteria, but unless someone is standing in the room from Medicaid, we will never know.

James Marx: I think somewhere in the prior authorization there should be a question asked if there will be someone there to monitor for adverse effects including hallucinations. At least you are putting them on notice, not just relying on the REMS program.

Holly Long: We could do something like Utah, they added the criteria that the health care setting must be certified by the Spravato REMS program.

Lisa Todd: More than what you have under number three, administered under the supervision of a provider. You're basically saying you need to be there to administer and watch them. To me that puts the liability on the provider.

James Marx: I think Utah is on the right track, I would like something along those lines added.

Dave England: I would like to add Carl's recommendation about being in consultation with a psychiatrist. I do have a question for the representative. The patient has to come in every two weeks for the administration? They have to be observed for two to four hours after. If the side effects persist, they continue to have the same side effect after the two weeks. Is there a time where treatment failure is determined? How do we know it is not working?

Stephanie Yamamoto: The administration has an initiation where it is given two times a week for four weeks. And then after that it is given 56 or 84 mg once a week. Then it can go to every other week. Our acute phase trials found statistical difference was after 24 days. That was the first two pivotal trials. Within 24 hours there was a statistical difference showing Spravato was effective at lowering the rates of MADRAS scores compared to placebo. The longer-term studies went out to 16 weeks.

Dave England: There wasn't a good time, even if monitoring, does the adverse events increase with continued administration?

Stephanie Yamamoto: It depends on the side effect. The blood pressure effect could occur at any point. The dissociation was mixed. They have not completed analysis of these. There were some that continue to have dissociation and that did not necessarily correlate with the treatment.

Paul Oesterman, Chair: Our three MCO's did respond with some additional recommendations. I noticed two recommended that it only be used in patients over 18.

Holly Long: I found that criteria for other states as well. Is that part of the FDA indication?

Carl Jeffery: Yes it is.

Holly Long: I would also like to mention that for recertification other states have 12 months, I saw three months or six months for recertification, but not 12 months. Could you provide guidelines for when they started taking it once per week?

Carl Jeffery: It is four weeks of twice weekly, then goes to weekly.

Holly Long: I would like to recommend something more realistic than 12 months.

Stephanie Yamamoto: The treatment went on for 16 weeks after the four-week initiation. If you think about the typical durations of depression episodes, they usually go to 12 months. What we found in claims is typical treatment durations don't happen longer than seven months. But it could be longer. There is not information that we have that says definitively that it would go longer than a year. It depends on the typical duration of treatment for depression.

James Marx: How does the potency compare to racemic ketamine? I see your max dose is 84 mg. Ketamine we usually use 120 mg.

Stephanie Yamamoto: The racemic ketamine is not technically studied in this population in a controlled trial setting. So, I am not able to answer that. Our studies were with esketamine and another antidepressant or the antidepressant alone.

James Marx: There is no Goodman and Gilman of ratio of potency?

Stephanie Yamamoto: You are looking at the gold-standard in trials, there is not a way to directly measure.

James Marx: With opioids you can measure different potencies.

Dave England: In the REMS, the patient goes back for follow-up, do they go through the MADRAS score? Is that part of the process for evaluation to continue?

Stephanie Yamamoto: The measurement based on criteria is not part of the REMS. The REMS, as we were working with the FDA, is really focused on reducing the abuse and misuse of this product. There are three parts to the REMS program, the pharmacy needs to be certified that they will only dispense it to a certified treatment center. The treatment center needs to be certified that they will fill out a monitoring sheet and send back to UCB, the program administering the REMS. And the prescriber also needs to certify they understand the REMS. It really is around the appropriate chain of custody as well as the monitoring.

Dave England: For patients with -treatment resistant depression, at what point do they decide to stop this medication? We know when to start it after failure of other agents. But once we start using it, at what point do we stop it because it is not effective?

Stephanie Yamamoto: I think looking at the acute phase three trials, it took 28 days for most to respond. The responders moved to long term treatment phase. We do still see some non-responders that turn to remission after that initial phase.

Beth Slamowitz: We currently have the recommendation for approval of 12 months. That could be shortened for evaluation.

Dave England: That is what I was going for. Three months or six months.

Paul Oesterman, Chair: Ryan you had some comments on yours.

Ryan Bitton: HPN put in 12 weeks initially and then reauthorization for six months thereafter.

Jim Tran: I read an additional warning about nephrotoxicity in pregnancy, is that part of the REMS?

Stephanie Yamamoto: I am not familiar with that part of it. Was that part of the package insert?

Carl Jeffery: It was probably in the binder.

Stephanie Yamamoto: It was not something that we included.

Paul Oesterman, Chair: Where we have the potential for the approval of the criteria, it says diagnosis of treatment resistant depression. Do we have that quantified in any way to define what is treatment resistant? It is a good product, but there are other products in terms of step therapy that maybe they could try that first for what duration before they jump to this?

Carl Jeffery: The diagnosis is out of my realm, but I think treatment resistant depression diagnosis has its own criteria.

Ryan Bitton: From HPN perspective, we help define TRD in our criteria as failure of three other agents. But we did not list any duration.

Dave England: I think we may want to add something to the criteria that the patient is not pregnant or if they become pregnant that they would discontinue this treatment.

Paul Oesterman, Chair: We can make that an exclusion criteria.

Holly Long: Is there a pregnancy rating?

Dave England: It says in the summary, it talks about the use in pregnancy.

Ryan Bitton: They don't really do pregnancy rating any more.

Dave England: It doesn't give a category any more.

Jim Tran: I think the FDA did away with the pregnancy category. It talks about the toxicity and the need for screening of patients.

Holly Long: I didn't see the pregnancy piece in any of the other states. But that makes sense if that is something you want added.

Paul Oesterman, Chair: I think for everyone's protection, may not be a bad idea. To recap at this point, I am hearing for the initial authorization, treatment resistant depression which one of our MCO's has defined as having failed three agents. Can we make a compromise to two agents?
Ryan?

Tom Beranek: SilverSummit has two agents. Mine is down a little further. Ours is two antidepressant failures.

Holly Long: Is that necessary or does that mean the same thing as the diagnosis.

Paul Oesterman, Chair: I think for clarification, it would be wise to have it listed in the criteria. The diagnosis of treatment resistant depression as evidence of failure of two antidepressants.

Tom Beranek: That is how ours reads.

Paul Oesterman, Chair: And then we would also have in the approval criteria, age 18 or over. Then for number four, be prescribed by or in consult with a psychiatrist.

Holly Long: Did you want the piece about pregnancy?

Paul Oesterman, Chair: Next is the exclusion criteria, would be pregnancy.

Beth Slamowitz: The package insert does have a statement regarding embryo fetal toxicity. It does say may cause fetal harm, consider pregnancy planning and prevention. It does not exclude it.

Paul Oesterman, Chair: Is there anything about breast feeding and lactation?

Beth Slamowitz: Not in the package insert. But in e-Pocrates, it does have the same language for lactation as well as for pregnancy or individuals of reproductive potential, consider avoiding. But it does not come right out and say it should not be used.

Paul Oesterman, Chair: Up to Date says the manufacture does not recommend in pregnancy. I would say an exclusion would be pregnancy and breast feeding and lactation.

Beth Slamowitz: So, we don't put too much in the criteria, if it is listed in the package insert and it is part of the prescribing recommendations for the psychiatrist or physicians, I don't know that we have to state it in the criteria. The assumption is they are prescribing appropriately within medical parameters. I don't want to bog down our criteria with information that is already out there.

Paul Oesterman, Chair: Maybe add to criteria number, the diagnosis of treatment resistant depression along FDA guidelines or something to that effect.

Holly Long: It is in the very beginning of Chapter 1200 where all the policy exists, there is an umbrella statement with that information.

Dave England: I don't have access to DSM criteria, but a quick Google from the Mayo clinic, treatment resistant has a lot of criteria that they apply. It talks a lot about switching agents and using something to augment. It says to consider phenotyping to make sure you can metabolize this. As long as that is all covered under treatment resistant depression, I think we have our bases covered. I can't find the specific DSM diagnosis of treatment resistant depression.

Paul Oesterman, Chair: We also have the re-authorization criteria. There was some discussion about changing the approval length to 12 month to three or six months. What is the feeling from the board?

Mark Canty: From a medical director standpoint, I would like to see the initial period shortened to something like Ryan is describing. You are saying the initial certification be 12 weeks?

Holly Long: The initial on here is four.

Carl Jeffery: The Optum criteria is four-week initial evaluation which is consistent with what Stephanie was saying. Most will respond within that time. There may be some that don't respond until they get to maintenance.

Mark Canty: So initially four weeks, and then for recertification will be longer.

Dave England: Go for six months.

Paul Oesterman, Chair: Six months sounds like the consensus. Then the approval criteria would be consistent with the initial criteria.

Holly Long: Would the board like to the sentence that we do with recertification where we like to see a positive clinical response to treatment?

Paul Oesterman, Chair: Yes. In the recertification criteria, showing a positive clinical response to treatment.

Holly Long: Do you mind going through each of the changes again?

Paul Oesterman, Chair: What we have for the prior authorization criteria for the initial authorization is for a four-week period. The approval criteria is a diagnosis of treatment resistant depression, patient is 18 years old or over. Number two and three remain the same. Number four is prescribed by or in consult with a psychiatrist. Then an exclusion criteria of pregnancy and lactation. For the reauthorization, the approval length was six months. The criteria point number five or in consult with a psychiatrist. Number six is to show a positive clinical response to treatment. Anything else from the managed care organizations?

Lisa Todd: Anthem as a couple other exclusions.

Paul Oesterman, Chair: Your exclusion include hemorrhage. Is that from the package insert?

Lisa Todd: I don't know.

Stephanie Yamamoto: It is.

Paul Oesterman, Chair: Then maybe we should include those with our other exclusion. The patient does not have an aneurism or AV malformation. With that being said, we need a motion to approve the initial and the reauthorization for Spravato with the criteria that we just delineated.

A motion was made and seconded. Voting: Ayes across the board, the motion carries.

- c. **For Possible Action:** Discussion and Possible Adoption of Prior Authorization Criteria and/or Quantity Limits for Gastrointestinal Agents Used for the Treatment of Chronic Idiopathic Constipation (CIC).

Paul Oesterman, Chair: Our next clinical presentation is the discussion and possible adoption of prior authorization criteria and or quantity limits for gastrointestinal agents used for the treatment of Chronic Idiopathic Constipation or CIC. It there any public comment? We will go ahead and look at our information here.

Carl Jeffery: We have criteria already for opioid induced constipation and irritable bowel syndrome. To round out everything, there is some cross-over with these other agents for chronic idiopathic constipation. There are a couple agents with crossover like Amitiza. I have the criteria listed on the screen.

Holly Long: Is what you are proposing to add to existing opioid induced constipation or the IBS agents or are we going to try to organize all three.

Carl Jeffery: It could be all under a gastrointestinal agent class. The criteria would be independent of anything else, but how it is categorized, it could be included with the other class, but it would be its own criteria. We put the criteria for 12 months for the initial authorization, a diagnosis of chronic idiopathic constipation, trial and failure or intolerance to lactulose and polyethylene glycol. And the requested drug is approved for the patient age because some are approved for different ages. I didn't include recertification criteria, it would be a 12-month approval with a positive clinical response.

Paul Oesterman, Chair: Do we want to include anything for the various agents to dose limitations?

Carl Jeffery: We do have some for irritable bowel syndrome.

Paul Oesterman, Chair: I think for consistency we should for this too. Tom, thank you for providing the information. What transpired in January 2019 that the use of most of these agents took a significant dive?

Ryan Bitton: That is the HPN slide, we had a formulary change.

Paul Oesterman, Chair: We have the prior authorization criteria with the proposal for a 12 month and same for the reauthorization with the diagnosis of CIC, trial and failure or intolerance to one of the following, lactulose or polyethylene glycol and then the requested drug is FDA approved for the patient age. And I think we were going to add the max dose for the various products.

Carl Jeffery: Did you already talk about the recertification criteria?

Paul Oesterman, Chair: It would match with the standard line with demonstrating a positive clinical response.

Tom Beranek: We had failure of a stimulant laxative too in addition to the two that are already listed.

Dave England: I like that criteria.

Paul Oesterman, Chair: We will add a stimulant class. I would assume most patients have tried a stool softener as well as a stimulant, at least we can document treatment failure. We have the criteria modified to add a stimulant laxative to bullet point number two, and the max dose bullet. We need a motion to approve this criteria.

Motion to approve the criteria made. Seconded. Voting: Ayes across the Board, the motion carries.

- d. **For Possible Action:** Discussion and Possible Adoption of Updated Prior Authorization Criteria and/or Quantity Limits for Anti-Migraine Medications – Serotonin (5-HT1) Receptor Agonists (triptans).

Paul Oesterman, Chair: Our next agenda item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for anti-migraine medications, serotonin receptor agonists. Is there any public comment?

Carl Jeffery: We are working through some of the old criteria that has not been reviewed for a long time. This is one of them. We thought it would be good to have the Board review and update if necessary. We did add the CGRP's at a previous meeting that prompted us to review the triptans too. I passed out the quantity limits for the antimigraine agents. These are what people can get now without a prior authorization. To exceed that, we have the criteria. If for any reason they need to exceed the quantity limits, they would have to meet these criteria.

Paul Oesterman, Chair: I want to go out on a limb, how many do we have that we have that exceed the quantity. I'm to the point that these medications are such that prior authorization may not be necessary.

Carl Jeffery: The criteria is just to exceed the quantity. These are pretty generous for most. When they move beyond this amount, I think it is worth evaluating. We don't see a lot, I don't have a number.

Beth Slamowitz: I don't think it is from a safety perspective but rather a stock-piling perspective.

Holly Long: We do have fairly consistent hearing prep meetings where we address criteria. There are times when these criteria come in handy and have taken this into consideration when we are really standing up for the safety of the recipient and the provider is not aware of the appropriate prescribing.

Jennifer Wheeler: I see in practice a lot of patients will get their refill with nine or 12 tablets, but then pay cash for the rest. Often they have a PRN attached to the refills. You can't see that on your side.

Carl Jeffery: I am showing on the screen the criteria that is in Chapter 1200. I did not propose any changes because we have not received any feedback of problems with the current criteria. As long as the board is ok with the current criteria, I think we don't need anything changed.

James Marx: One thing I notice, in the criteria is there are no more than 15 per month, yet none of the dispensing limitations would allow anywhere near 15, the most would be 12. Many times, it takes two doses to treat a headache. This limit is already way above of what were are providing.

Carl Jeffery: The criteria is not to exceed 15 per month. The criteria is for exceeding the quantity. They need a PA is to exceed that amount, so if they have eight migraines per month, they need a PA. If they are exceeding 15 per month, they probably need to see a specialist.

Paul Oesterman, Chair: You are asking that we re-approve the existing criteria for exceeding the quantity limit? Could we have a motion to approve the existing criteria having reviewed it?

Motion and second to accept the criteria as presented. Voting: Ayes across the Board, the motion carries.

- e. **For Possible Action:** Presentation, discussion and possible adoption of updated DUR bylaws.

Paul Oesterman, Chair: That completes our actions for the clinical presentations. We now have some possible action for a revision of the DUR Bylaws. If the audience wishes to stay, you are more than welcome. There are some significant bylaw changes. Holly, I will turn it over to highlight the changes just general information. This is going to be a preliminary change, there will be some additional changes for the next meeting.

Holly Long: Julie is helping out as far as being an expert in open meeting law. I am looking forward to her assistance going forward. That will be for the next meeting. First of all, I tried to make sure that everything is in color so you can see what information is new or what has been relocated. The red text is new, the red with a line has been removed and green has been relocated. We now have a cover page and table of contents. The third page includes the purpose and mission statement. We also updated the definitions found on the fourth page. One of the main items I wanted added was the definition of “Actively Practicing” practitioner. We referenced the NRS here, but just so everyone is clear, you do have to be an actively practicing practitioner in order to be a board member. At any time, if you retire, have your license suspended, you need to let us know so that we can remove you from the Board.

Paul Oesterman, Chair: For clarification, actively practicing within the State of Nevada, correct?

Holly Long: That is correct. Moving along on page five, there is added clarification of the Federal regulations within legal authority. Under appointment, we also updated anywhere where it was listed the title of the DHCFP Coordinator which was previously Duane Young it needed to be updated with Beth Slamowitz. That has been updated to DHHS Senior Advisor for Pharmacy. On page six, section three, the conflict of interest, the first reference is to the DUR Board disclosure agreement. That is the last page of the entire document. This is something that many other states have done and we wanted to do too. Most of the information is not anything new, but we are going to be require all the board members sign this. We will do this at appointment and reappointment. I am going to hand out one for signing today.

James Marx: In ten years, I have not seen anything that is not confidential that should not be disclosed. I am not sure what I am not supposed to be disclosing? Have we discussed items in the past that we should not be discussing? I’m baffled by this requirement that is a solution to a problem that doesn’t exist.

Beth Slamowitz: I don't think this is in reference to the information in the binder, which is a public document. The disclosure statement and the reason other states have it is for the board members to disclose their affiliations. Any cooperation they may have with drug manufacturers or associations. A lot of that information is Federally reported anyway. This is just in addition to that to what is already in regulations. It is more or less an attestation.

James Marx: If that is required, then somehow, any confidential information should be in italics or something. We don't know what we are not supposed to disclosed.

Beth Slamowitz: I think we may be passing each other. It is not what is in the binder or what is talked about within the meeting that is a public meeting.

James Marx: What does it refer to?

Beth Slamowitz: Maybe it will help to read the statement. Then you can ask any clarifying questions. Holly, could you please read the statement?

Holly Long: The DHCFP and the Drug Utilization Review Board (Board) are not bound in any way by any statement of action on the part of any Board member except when a statement or action is in pursuit of specific instructions from the DHCFP or the Board. The Board and its members may not claim or appear to represent DHCFP or the Board in any legislative or advocacy activity without approval from the DHCFP Coordinator and the Director. A member may, however, represent him- or herself or another entity in the legislative or advocacy process. A Board member may not accept payment for services that are requested because of the members' title or position on the Board. A Board member should not accept or solicit any benefit that might reasonably tend to influence the member in the discharge of the member's official Board duties. A Board member should not knowingly solicit, accept, or agree to accept any benefit for having exercised the member's official powers or duties in favor of another person. A Board member shall make themselves aware of and follow Open Meeting Law policy as set forth in chapter 241 of the Nevada Revised Statutes as it applies to the Drug Use Review Board. Nondisclosure Agreement: A Board member may not disclose confidential information or agency-generated information in draft form acquired through his or her board membership, unless DHCFP has released and made public the information or document and/or the DHCFP Coordinator has approved the release in writing. This requirement survives the member's tenure on the Board. For purposes of the Nondisclosure Agreement, the term "confidential information" includes all information protected by the Health Insurance Portability and Accountability Act (HIPPA), information that has commercial value or use, such as trade secrets, and information communicated in the confidence by the DHHS System. Conflict of Interest Statement: I agree to disclose any current affiliation with a business or corporation that manufactures prescription drugs. This includes direct compensation through employment and contractual activities.

James Marx: What you mentioned, I have never seen anything that was so privy to non-disclosure, how would we know if we have some of this information that should not be disclosed? I do non-disclosures all the time, I don't see anything here that we discussed that should not be disclosed.

Paul Oesterman, Chair: I think the term non-disclosure means multiple things. You're talking about disclosing information that is already public. I think the intent here is that we agree not to get paid off by any of our drug...

James Marx: That is something else.

Paul Oesterman, Chair: I think that is what this is referring to.

James Marx: That is conflict of interest.

Holly Long: I included several agreements on this, and it is actually titled, “Disclosure Agreement.” Within the disclosure agreement, there is a non-disclosure agreement and there is a conflict of interest statement. I have a few things I am trying to support all within one document.

James Marx: But that is two different issues, that is the problem. Am I off base here?

Julie Slabaugh, DAG: I don’t know enough about what information the board receives from the agency that is considered confidential.

James Marx: I have never seen anything of that nature. I wouldn’t know if I received that information in the past. We need to have a mechanism to notify us if we received confidential information.

Beth Slamowitz: Under normal circumstances, we would make that statement. If we are in the public meeting and abiding by open meeting law, the information is public. If we are having another discussion and we purposely make the mention that this is confidential or draft or should not go to the public. That is what we are referring to.

James Marx: Is that going to be part of the discussion now? I have never seen that happen in ten years.

Beth Slamowitz: It may not happen for another ten. The bylaws have not been updated since the board was created. There is a need to update the bylaws to align with what some of the other states are doing. There is language about representation for the legislature. Many of you work outside of this board and there may be groups that you are involved with. I think it is to protect the information and as an understanding of what your participation and expectation is as far as confidentiality.

James Marx: I’m not sure what information, I have never seen confidential information.

Beth Slamowitz: But there could be. We are trying to set ourselves up for future meetings. If information is confidential, we have said it is, and it gets out, we have this agreement to back up DHCFP.

James Marx: We don’t have to worry about anything that has happened anything up to now.

Beth Slamowitz: Yes, this is a go-forward change. It will be at your appointment and reappointment.

Dave England: For example, if I was doing a presentation that I wanted to incorporate some of the information we discussed here.

Beth Slamowitz: As long as it is public information, it is yours to use. The information we share publicly is aggregated and de-identified.

James Marx: I don’t think we should ever have patient information on any of the reports.

Beth Slamowitz: I think we would be restricted by HIPPA and open meeting laws anyway. But sometimes we have discussions outside of this meeting.

Paul Oesterman, Chair: You want copies signed today correct?

Holly Long: Yes please. I will reach out to the members who are not here.

Beth Slamowitz: At reappointment, we will ask you to sign again.

James Marx: Can we sign it electronically? We are not supposed to be using paper.

Beth Slamowitz: We will be using paper today for this.

Brian Le: I have a question on the conflict of interest. I do research for different companies. Does that mean I have to disclose that?

Paul Oesterman, Chair: If we were to discuss a product for which you are doing research for that particular product or company, you would want to recuse yourself from that discussion. I have done that before and I have just recused myself from the discussion.

Holly Long: You can still participate in the rest of the meeting, you just can't be a voting member for that discussion. One of the biggest topics is a conflict of discussing cost. In reviewing the NRS and operations manual, we are not to talk about cost. You don't want to base your decision on cost. There was conflicting information that has been fixed. As far as the terms, there is some language within the terms that I removed. Where it has information regarding even and odd-year terms, that language is confusing and is not in NRS anywhere, so that has been removed. Terms will still be for two years. We added that the terms will be for two years, but no more than three terms consecutively. You won't be a board member for more than six years in total. Every time you are up for reappointment, it is at the discretion of the Director. That is new language.

Paul Oesterman, Chair: Lets go back to that point. There are at least three of us here that have been on the board for 15 years. Can we get some direction from the Director?

Holly Long: Going forward. There are a number of members that have been here for quite some time. This will be a go-forward change. You won't be removed from the board because you have been here for over six years. But at reappointment is up to the Director. But from here on out, you won't be reappointed for more than three terms, or six years. The other piece, I added language for board member removal. One piece that was very important, we have had some trouble with participation. It has always been expected and encouraged that board members participate. The Director asked that we include specific language that outlines how many meetings can be missed before we ask you to not be a board member any more. It allows us to evaluate if this is a good fit for you. Sometimes people just take on too much. If you miss three or more meetings and then in another section it states expectation that you are here for at least 50% of the meetings. We would not look at removing unless you miss three or more within 12 months. Under article four, under Functions and Duties, we added defining and clarifying language, you will see that in green. That was relocated for organization. The public comment part that Julie has brought up as not aligning with open meeting law. The public comment part is the piece that we will be updating, and I am working with Julie to assure we are aligned with open meeting law. That will be addressed within the bylaws and that will also be addressed in the Medicaid operation manual so that everything is in alignment. You will see that at the next meeting. I will let you go through and ask any questions. As of today, the Bylaws will be effective. The Director has already approved these and we will re-agendize them for the additional updates.

Paul Oesterman, Chair: Do we need to approve these?

Julie Slabaugh, DAG: Yes, they do need to be approved.

Paul Oesterman, Chair: We have these revised and updated Bylaws. Thank you for all your efforts and hard work.

Holly Long: Thanks, I hope they look better. This has been a big task, they were really a mess. I tried to make them easier to read for the Board and the public. I am open to suggestions if you want to email me.

Jennifer Wheeler: On page five, under section A. There is a lot of private practice and some hospitals going away from accepting Medicaid. Would it be appropriate to include an affiliation requirement?

Holly Long: Julie, do you understand what she is asking? She is suggesting the members service Medicaid members.

Jennifer Wheeler: I have seen more concierge medicine, that obviously would not serve Medicaid.

Beth Slamowitz: You are saying that the board members actively see the Medicaid population?

Julie Slabaugh, DAG: I could see if that applies. This is more restrictive, I am not sure that would fly. It makes sense.

Beth Slamowitz: That would be our hope and recommendation. I am not sure what support and buy-in you have if you were not seeing Medicaid patients.

Dave England: If you are in concierge medicine, you are still practicing in the environment, you still have impact and concern how care is being provided in your state. That would be fixing some bias into the committee if you have to be a Medicaid provider. I have worked for both for-profit and non-profit and Medicare and non-Medicare, I don't know that would be a requirement I could support.

Julie Slabaugh, DAG: If you were not practicing, you could say the same thing. That doesn't mean you are not a qualified clinician.

Beth Slamowitz: The purpose of the board is to give recommendations to the state for drug utilization for the Medicaid population. If you are not actively working with the Medicaid population, I am not sure those recommendations are necessarily backed by experience. It is good to have a mix of opinions, but to Jen's comment, it is definitely something we would prefer and encourage.

Holly Long: I have seen some other Boards, like the MCAC Board. NRS dictate each position is specific including a Medicaid recipient. One is a pharmacist, one physician, one in expertise in psychiatry. Where ours is 51% physician or 51% pharmacist. If we could not require everyone is, maybe we could require a percentage. I do try to get a diverse expertise for the Board. I do run into recruiting issues to try to accomplish this. We also try to support rural areas, North, and South Nevada. Any other comments on the Bylaws?

Paul Oesterman, Chair: We need to vote to approve.

Holly Long: I will be updating this and attaching it as an attachment for the next meeting agenda.

James Marx: Do we vote on this or does the Director approve these?

Holly Long: For now, the existing language we need to have you vote and approve.

Motion made to approve the bylaws as presented, seconded. Voting: Ayes across the Board, the motion carries.

5. Public Comment on any DUR Board Requested Report

Paul Oesterman, Chair: Now we will go to the standard reports. The first one being our opioid utilization, top prescribers and members. Do we have any public comment? We do have one person on the phone.

Khan Pham: My name is Khan Pham, I represent the Nevada Pharmacists Association. You are doing a wonderful job of taking care of the patient. On the email I addressed to Dr. Marx. On behalf of the independent pharmacies in Nevada, the question why do you allow your members to have limited options to care when the reimbursement is so negative. I know this is not your responsibility.

Paul Oesterman, Chair: Hi Khan, this is Paul the chair...

Julie Slabaugh, DAG: This is Julie Slabaugh, as a member of the public you can comment on anything that may or may not be on the agenda. However, under the Federal rules and the statutes governing this board, they cannot discuss cost. So, they cannot have any interaction with you regarding your public comment.

6. DUR Board Requested Reports

a. Opioid Utilization – Top Prescribers and Members

Paul Oesterman, Chair: Any other public comment. Ok, thank you. Now we will move to our DUR Board requested reports. The first being the opioid utilization, top prescribers and members.

Carl Jeffery: On page 158 is where the standard reports start for fee for service. On the first report, the fee for service, this is the opioid utilization trend. This is the standard format we have been using.

Holly Long: Are the dates accurate for the quarter? January to March?

Carl Jeffery: It shows April through March, but it is the full year. It is just the quarterly DUR report. The title is not exactly consistent with the data.

Beth Slamowitz: There is the report period date. This is for the whole report period? This is for whole report period.

Carl Jeffery: This the template that was provided.

Lisa Todd: I think the next reports are broken down by quarter. It is an all-year summary for the whole year and then everything else is quarterly.

Carl Jeffery: This is the full year. It includes more data than what the title shows.

Paul Oesterman, Chair: Is there anything out of line? It looks like the overall trend is consistent with what we are hearing with opioid related deaths. Our usage is trending slightly downward.

Carl Jeffery: That is consistent with what we are seeing too. The trend continues to go down. Opioid prescribers for the current quarter. Not much has changed vs. the past quarter. The top quarter is the most recent January through March and then the next is October through December

2018. We hide the prescriber ID's, but the encrypted ID's match up. They do shuffle around a little bit, but it is pretty steady. I did carry it down to page 160, the opioid by member, the prescriber ID will match the top prescribers. Not very many of them cross over, there are only two on the fee for service. I put the opioid utilization in a chart on page 162, that is a little better for seeing the downward trend. Usually January is always a spike.

Paul Oesterman, Chair: Is that new members?

Beth Slamowitz: I don't think it is new members because we do not have the same annual enrollment. I think usually what I see is a spike around that time of year is the holiday trend and use. You have higher levels of depression and anxiety and it trends with opioids around that time of year.

Lisa Todd: The other thing that sometimes effect data is the fact that February being a short month and January being 31 days, that can really throw it off just enough.

Paul Oesterman, Chair: Curious with the rolling membership, you may in December have some that lose their coverage, do you find an increase in membership in January?

Holly Long: It is pretty consistent monthly.

Beth Slamowitz: If anything, we see more of a trend during the summer time with enrollment spikes.

Carl Jeffery: I also broke down the top ten members by what they are taking. I have the member encrypted ID's, the drug name and quantities they are getting. That concludes the fee for service data. Any questions.

Brian Le: Can we go back to the provider list. I am not sure why they are prescribing that much narcotic. I do pain medicine, this is excessive. This is worrisome. For the maxillofacial surgeon.

Carl Jeffery: I noticed something funny because this popped up somewhere else. The specialties in our system are self-reported. When I look him up on line, he is a pain specialist PA.

James Marx: It could be a wrong classification.

Holly Long: There is not a requirement to call out a specialty or certification. Many times we are Googling these to see what their specialty is. It is difficult to find sometimes.

Carl Jeffery: Often we don't know if they work in a pain clinic, we don't know if they are certified.

Holly Long: So many of them may work in three of four areas within the same clinic. You might work in pain management but help with another area too. Annually for the last few years we have used the top prescribers, we created a letter to the top ten letting them know where they stand among their peers. We have only had one response.

Carl Jeffery: We sent the letter to a PA and their attending physician responded defending their practices.

Holly Long: We don't ask for a response, but it was nice to hear back. The last time, we did not receive any feedback. We would like to continue sending the letters.

Paul Oesterman, Chair: For a future meeting, is it possible to do a cross-over report for the top opiate prescribers and see if we can do a top benzo prescriber to see if there is cross-over?

Dave England: Sending these letters out to prescribers, is one reason we are not getting a response back, I'm curious if they did respond, are they construing that as an admission?

Carl Jeffery: We don't ask for a response. This one prescriber felt they should defend their prescribing. That midlevel is no longer on the top ten list. I don't know if that is good or bad, they may have stopped seeing Medicaid patients. I think we need to be careful with these letters.

Dave England: We need to let them know what we are seeing. This really isn't a request to stop prescribing, but to make them aware. It is kind of frustrating to send these letters out and not get any response.

Holly Long: We had to get the letters approved by each DAG that support the meetings. Adding the additional information asking for feed-back was not approved. We could try again.

Dave England: I think the feedback would be good as they see it. We don't see it as a problem.

Paul Oesterman, Chair: I think we should continue to make it an educational opportunity. Maybe we can provide some education to use. Is there a specific population you are seeing? Is there anything we can do to assist in your practice?

Beth Slamowitz: Many states are doing report cards where they are sending high prescribers, similar to our letters, but where they fall in the whole state. That is a bigger story to tell. I think we are heading in that direction to use some of the PDMP data more appropriately. I would not have high expectations that even if we ask for feedback, we won't hear back. They are all busy, and the last thing we want to do is add something else to their plate. I think it is best to let them know we are following it.

Dave England: Are we working with the board of pharmacy and nursing?

Beth Slamowitz: The board isn't currently doing anything, but that is why we are working with them with what the PDMP can do in the future.

James Marx: I can tell you the utilization of the PDMP is limited by statute, that is going to be one issue you are going to have to address. The use of it is very strictly controlled. I think when you look at raw numbers, it can be misleading. Sending them a letter saying they wrote a lot. This is why it is important to get the area of practice. Without the context, these numbers are meaningless. If you had that information and it was correct, then you could let them know where they sit among their peers within their specialty.

Beth Slamowitz: That is the hope and approach for using the report cards. First is using our Medicaid data. If we are not getting value from these letters, we can stop sending them.

Holly Long: Any other questions?

Lisa Todd: Our opioid utilization data seems to be trending down as well. We have a decrease in member count and the claim count has gone down. But when comparing the claim count and member count for both of those months, the number of prescriptions the members are getting is consistent. I think we are similar to fee for service data. The top opioid prescribers, I put the prescriber type, I didn't go into their specialty. One thing I noticed is that we have about the same five to six prescribers that are in this data. I did include four quarters of data. No one really stood out when looking at the physicians.

Paul Oesterman, Chair: I find it interesting that all your prescribers are in the Southern part of the State.

Carl Jeffery: Where does most of the population live for Amerigroup?

Lisa Todd: I don't know for sure. I think we do have more in the South.

Brian Le: I think some of this data is misleading. What we should look at is the MME.

James Marx: I agree. I encounter this because I write high quantity but low doses. This is better because it decreases the risk of drug liking. I think looking at dosage counts is misleading.

Lisa Todd: I think that is a good point.

Paul Oesterman, Chair: I think for future reports if we can include MME's, that would be good.

Lisa Todd: We do calculate the MME every time we get a claim for an opioid. I think our limit is set to 120 mg.

James Marx: I think the whole quantity limit issue comes in here because it pushes prescriber to write for higher dose with a lower quantity.

Paul Oesterman, Chair: So future reports to be based on MME's.

Beth Slamowitz: I think if we go down that path, each program should identify their limitation so you can relate that to the data. We could add an additional column for MME.

Carl Jeffery: If you look at prescriber, you would look at the total MME for that time period. It is going to be a big number. But it will be a better comparison.

Brian Le: You can do MME per member too.

Beth Slamowitz: Yeah, and that will be an average for that member too. I'm not sure how much use that will be. But if we include the total, then we can back in to other data.

Lisa Todd: I broke down the top ten utilizers. I did find it interesting, of our top ten prescribers, there were only a handful of those for the top ten utilizers. I'm taking that back to dig a little more to look at some of this data. On member 628, there are several prescribers and I think there are not any of those in the top ten list. The next page is the members broken down by the meds they are on.

Tom Beranek: For SilverSummit, pretty much what the first two talked about. We have a downward trend too. The member count and claim count for January through March, maybe February having less days had something to do with it. Overall a downward trend. The top ten prescribers, nine of the ten were on the previous quarter. We had one anesthesiologist added and one pain management prescriber exit. We will add the MME for next month. On the opioid utilization by member, we have 25 members here. About half and half about prescribers on the top ten. We had one prescriber show up on nine of the top members. We are having the investigations unit taking a look at this prescriber. I don't have anything to report yet.

Ryan Bitton: For HPN, we see a similar trend. Looking at April to March is a 12% decrease in total scripts. The top prescribers are pretty consistent. Most are in the South, provider D is in Reno. The top 25 patients, 11 are seeing three of the top ten prescribers. Number M22 is concerning because they are seeing a lot of prescribers, even though they are just one-time fills.

They have been added to the lock-in program, not because of this report, but through other reporting. Each prescriber is highlighted if they were on the top ten.

Paul Oesterman, Chair: You mention the lock-in program, that is something we have not talked about for a while. I think it would be good to get an update.

Carl Jeffery: What specifically do you want to see?

Paul Oesterman, Chair: Are there new members added to the program?

Beth Slamowitz: We don't terminate anyone out of the lock-in program. We don't have any policy to do that. Yes, there are always new members, we have updated reports every month. The department reviews reports from Optum and decides who should be added to the program.

b. Opioid Use Disorder and Opioid Use

Paul Oesterman, Chair: Maybe just a graph of count of members in the lock-in program. Now we have opioid use disorder and opioid use.

Carl Jeffery: We summarized these a little. The Board wanted to see how many members have a diagnosis of opioid use disorder and who are receiving an opioid. The report starts on page 180. Members with a diagnosis of opioid use disorder is 10,805. Of those members, we looked at who was getting an opioid and who is receiving medication assisted treatment. On page 182, these are the top 25 members getting medication assisted treatment with the products.

James Marx: I'm shocked at the number of patients with opioid use disorder and how few are on Suboxone or Sublocade.

Carl Jeffery: On page 180, members with a diagnosis getting an opioid is 4,092, those getting MAT 193. We are not talking about very many people.

James Marx: I wonder if that diagnosis is correct. Technically, you have to have pretty good justification to prescribe someone with this diagnosis an opioid. We have such a low number getting treatment. Something is wrong with those numbers.

Beth Slamowitz: This is a one-year time period, is there a potential they could have had an opioid in March then they were on treatment in November. So, within the data it looks like they were on both, but they were not on it at the same time.

Carl Jeffery: Right, we don't have the dates on there, but you can see members with both oxycodone and Suboxone. We did a retro-DUR activity where we looked for members who were getting MAT and an opioid. We didn't find anyone. So, I think the providers are doing pretty good with not using these together.

James Marx: It is not so much that they are getting Suboxone. I have some that are on Suboxone for pain and getting oxycodone for breakthrough. There are studies showing this practice, so that isn't terrible. I am concerned with the total number of patients getting Suboxone in general. I am a big fan of using these products for treatment.

Beth Slamowitz: I think it will be interesting to review this data after the April changes are effective where we removed the PA criteria for Suboxone. For MAT treatment, I am not incredibly surprised by these numbers. We don't have a lot of prescribers that want to do MAT treatment. We are working on policy that will reflect the requirement for the SUPPORT Act. It will be interesting to see the trend as some of the policy changes.

Paul Oesterman, Chair: Do we have any data in terms of naloxone prescriptions?

Beth Slamowitz: Yes, through the Department of Behavior Health. Is there something specific you are looking for?

Paul Oesterman, Chair: I think if we could see who is getting an opioid with a naloxone rescue.

Beth Slamowitz: We can look at it from hospital claims and hospital claims.

Paul Oesterman, Chair: Point of sale claims.

Dave England: If we look at the number of members with a diagnosis of opioid use disorder, this is over a year, I wonder if the time is throwing off the numbers. Maybe some people have dropped off the program.

Carl Jeffery: A diagnosis does not follow the patient like an opioid does. If one prescriber diagnoses the patient, another prescriber may not know they have that history.

Beth Slamowitz: It makes you questions if the prescribers are reviewing the PDMP. I think even without the diagnosis, they could identify a problem.

Brian Le: Even if we check the PDMP, we don't know if another provider made that diagnosis.

Paul Oesterman, Chair: Down the road, will we be able to run parallel reports with the PDMP and see if the PDMP has been checked?

Beth Slamowitz: We tried to get legislation to have all medications in the PDMP so emergency rooms and hospitals would also have that information. It was shot down. It does not mean we will not try again, I think there is some benefit to your point for every prescriber to have the information in front of them and including the diagnosis.

James Marx: What happens with the emergency rooms having access, there was not any change to treatment based on what was on the PDMP.

Beth Slamowitz: I think it came from the retail association and some privacy issues.

James Marx: It goes the other way too, if you see an overdose diagnosis, the pharmacist may not want to dispense the prescription.

Beth Slamowitz: There is a potential, but we need the legislation to allow access.

Lisa Todd: I pulled the data similar to fee for service. We didn't have anyone with an opioid and MAT with the diagnosis. My report is grouped a little different.

Paul Oesterman, Chair: You have the data, we heard a case where you isolated the data. Is there any action you have taken with this data?

Lisa Todd: We referred some cases to our investigation unit.

Ryan Bitton: We did not do anything with this data, but because of other reports. We have system edits in place to stop and validate these.

Lisa Todd: We do have opioid use retro-DUR programs and we review that type of data. But I have not turned this specific report over to anyone.

Tom Beranek: Part of our lock-in process has to do with this same information. We don't use this report. But we have another report with the diagnosis and use and we bring 15 candidates per month for consideration for lock-in.

c. Specialty Drug Utilization

Paul Oesterman, Chair: We're down to specialty drug use.

Carl Jeffery: This was another board requested report. A specialty drug is anything with special monitoring or limited distribution or administration. Lovenox does require some special monitoring and administration, it is our number one by count. Avastin is a little different, it is used for chemotherapy and also used for macular degeneration. Looking at the paid amounts, the hemophilia drugs are always number one.

Paul Oesterman, Chair: On the claim counts, Aranesp, can we see how many of these members are on dialysis.

Carl Jeffery: It should not be very many because this is included in the PPS rate for dialysis centers.

Paul Oesterman, Chair: It just seems like a lot.

Carl Jeffery: Looking at the top 25 by paid amount, not much is surprising here.

Lisa Todd: For Anthem, most of the drugs we see are the HIV and Hep C type medications. It has been the trend recently, some of our diabetic medications are in there too. I didn't see anything really standing out. The same five drugs are in both list by claim count and amount paid.

Tom Beranek: For SilverSummit, the primary drivers are HIV and Hep C. Humira is climbing as new indications are approved. Otherwise, nothing really stands out. From the cost, Mavyret is on the top for us and then HIV. I don't see the hemophilia that fee for service sees.

Carl Jeffery: Is there some eligibility thing that pushes the hemophilia patients to fee for service?

Beth Slamowitz: I think there are other comorbidities that make them fee for service eligible.

Ryan Bitton: HIV and Hep C and Humira like SilverSummit. We have some transplant medications in the specialty bucket, so they show up here. Not trends that are alarming.

7. Public Comment on any Standard DUR Report

8. Standard DUR Reports

Paul Oesterman, Chair: Let's wrap it up with our standard reports. Do we have any public comment?

Carl Jeffery: Quarterly reports for fee for service. We have top ten by paid amounts, almost all are specialty. Then we have top ten by claim count looking at current quarter and previous quarter. We get some of the chemotherapy agents included. The anticonvulsants have overtaken opioids by quite a bit. Opioids have fallen down the list.

Paul Oesterman, Chair: Have you seen any changes in practice with the quinolones.

Carl Jeffery: We turned that edit on in May, so it won't show on this report.

Paul Oesterman, Chair: At the next meeting, can we see a report on how that was impacted?

Lisa Todd: I think everything is consistent with the others by paid amount. Antiretroviral like HIV meds. Some of our diabetic medications. One of the bigger trends is some of the new more expensive antidiabetics, there are some providers skipping some of the older cheaper drugs and going right to the new expensive drugs. Nothing else really stands out.

Ryan Bitton: For HPN, this is pretty consistent quarter to quarter. Opioids are going down and NSAIDs and asthma before opioids. Nothing else to comment on.

Tom Beranek: I can copy Ryan this time. NSAIDs are up there for us. Glucocorticoids are up there this time. Other than that, no big difference. We did have hemophilia show up more last year than this year. Insulin is up on the list.

Carl Jeffery: The pro-DUR edits is next. I don't think I need to point out anything weird.

Paul Oesterman, Chair: Managed care organization, anything that stands out?

Lisa Todd: Not for Anthem.

Ryan Bitton: Not for HPN.

Tom Beranek: Not for SilverSummit.

Carl Jeffery: For retro-DUR, for fee for service, we continue to work on a few things. We are looking at antianxiety combinations, high dose zolpidem in women. Top ten opioid prescribers. We looked at topical doxepin from compounding pharmacies, but were not able to identify anything with those claims.

Lisa Todd: I listed one, the non-adherent to medications. We have several programs, this is just an example of one. We notify the prescriber and members if we notice they are late with refills.

Paul Oesterman, Chair: What does the NA mean on some of the responses?

Lisa Todd: That means we don't have responses collected yet.

Paul Oesterman, Chair: I'm curious, when did the letters go out that you have not received responses.

Lisa Todd: They would have gone out in the time frame, but the team that does these did not have this information. I can bring that back.

Paul Oesterman, Chair: Please do, that seems like it should be available.

Lisa Todd: I know we usually track if we have seen an improvement. Many times programs look at six months to close it out. It may just be the numbers are not complete yet.

Ryan Bitton: I will call out just a few. We do the programs by the quarter. The PBM does not report back the response rates in the same quarter, that is why we see some TBD on our report too. We have some HEDIS measures for short acting albuterol or high blood pressure treatment.

Tom Beranek: We focused on hypertension in the first quarter. We identified patients that were not compliant. We chose a number of members to write letters or call if they are more critical. We are getting some information from the PBM that is not entirely accurate, so we are working through some of that.

9. Closing Discussion

Paul Oesterman, Chair: In closing, do we have any public comment? Our next meeting is scheduled for October 17, 2019. Same time and same place.

The meeting adjourned at 3:44 PM.

Zolgensma
(onasemnogene
abeparvovec-xioi)





Prior Authorization Guideline

Guideline Name Zolgensma (onasemnogene abeparvovec-xioi)

1 . Indications

Drug Name: Zolgensma (onasemnogene abeparvovec-xioi)

Indications

Spinal Muscular Atrophy (SMA) Indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. Limitation of Use: • The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated. • The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

2 . Criteria

Product Name: Zolgensma

Approval Length	1 Time Authorization in Lifetime
Guideline Type	Prior Authorization

Approval Criteria

1. The mutation or deletion of genes in chromosome 5q resulting in one of the following:
 - a. Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13)

OR

- b. Compound heterozygous mutation of SMN1 gene (e.g., deletion of Survival of Motor Neuron 1 [SMN1] exon 7 [allele 1] and mutation of SMN1 [allele 2])

AND

2. One of the following:

- a. Both of the following:
 - i. Diagnosis of symptomatic Type I or Type II spinal muscular atrophy (SMA) confirmed by a neurologist with expertise in the diagnosis of SMA

AND

- ii. Patient is less than or equal to 2 years of age

OR

- b. All of the following:
 - i. Diagnosis of SMA based on the results of SMA newborn screening

AND

- ii. Patient has 3 copies or less of Survival of Motor Neuron 2 (SMN 2)

AND

- iii. Patient is less than or equal to 6 months of age

AND

- 3. Patient is not dependent on either of the following:
 - a. Invasive ventilation or tracheostomy
 - b. Use of non-invasive ventilation beyond use of naps and nighttime sleep

AND

- 4. Submission of medical records (e.g., chart notes, laboratory values) documenting patient's anti-AAV9 antibody titers are less than or equal to 1:50

AND

- 5. Patient is not to receive concomitant SMN modifying therapy (e.g. Spinraza)

AND

- 6. Prescribed by a neurologist with expertise in the diagnosis of SMA

AND

- 7. Patient has never received Zolgensma treatment in their lifetime

Spinal Muscular Atrophy (SMA) Agents

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Summary

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
SPINRAZA	10	31	1079	155

Date Filled	Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
201807	SPINRAZA	4	4	128	20
201808	SPINRAZA	5	5	170	25
201809	SPINRAZA	3	3	102	15
201810	SPINRAZA	4	4	136	20
201811	SPINRAZA	1	1	34	5
201812	SPINRAZA	5	5	170	25
201901	SPINRAZA	2	2	35	10
201902	SPINRAZA	4	4	136	20
201903	SPINRAZA	1	1	34	5
201904	SPINRAZA	5	5	236	25
201905	SPINRAZA	3	3	102	15
201906	SPINRAZA	1	1	34	5

* No Claims for Zolgensma

Narcolepsy Agents





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

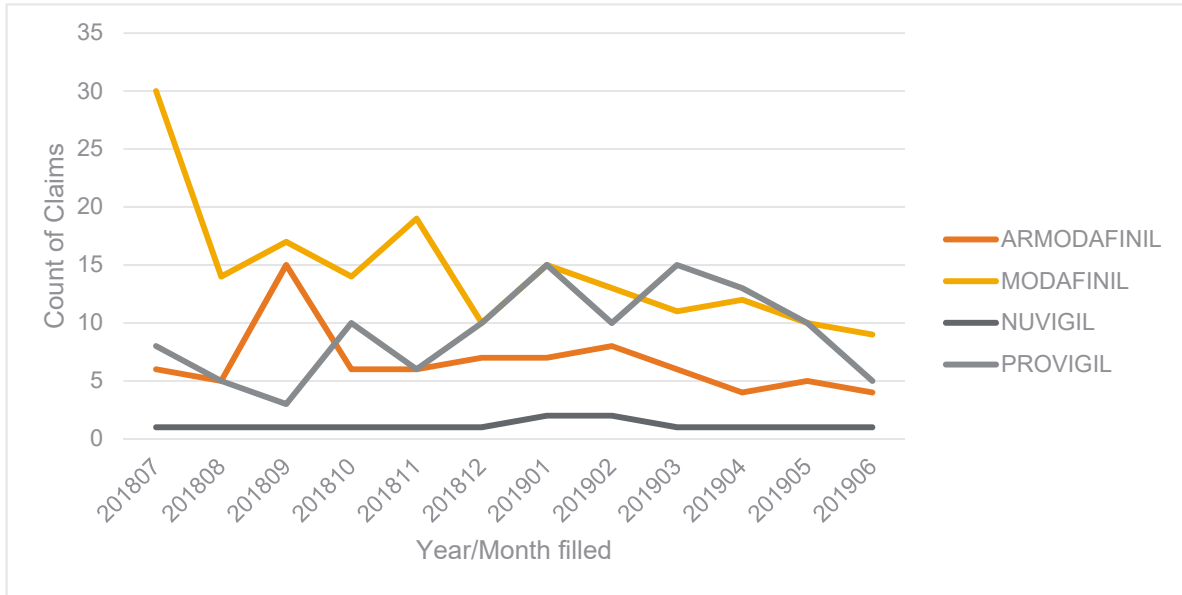
- 2** Patient continues to be fully compliant with ongoing treatment(s) for the underlying airway obstruction (e.g., CPAP, BiPAP)

Narcolepsy Agents

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
NUVIGIL	1	14	370	740
PROVIGIL	21	110	2,413	2,803
MODAFINIL	34	174	4,351	4,842
ARMODAFINIL	12	79	2,109	2,109



* No claims for Sunosi

DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

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 difference 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 (Alshaiikh 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	<i>Narcolepsy or OSA</i> : once daily in the morning. <i>SWD</i> : 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	<i>Narcolepsy or OSA</i> : once daily in the morning. <i>SWD</i> : 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	<i>Narcolepsy or OSA</i> : 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.

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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.	<p>Patients with hepatic impairment should reduce the starting dose by 50%.</p> <p>When using concomitantly with divalproex sodium, an initial dose reduction of at least 20% is recommended.</p>

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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Publication Date: June 7, 2019

Hematopoietic/Hematinic agents



Prior Authorization Guideline

Nevada Medicaid Fee for Service

Guideline Name Erythropoietic Agents

1 . Indications

Drug Name: Aranesp (darbepoetin alfa)

Indications

Anemia Due to Chronic Kidney Disease Indicated for the treatment of anemia due to chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis.

Anemia in Cancer Patients on Chemotherapy Indicated for treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and upon initiation there is a minimum of 2 additional months of planned chemotherapy. Limitations of Use: Aranesp has not been shown to improve quality of life, fatigue, or patient well-being. Aranesp is not indicated for use: (1) In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy; (2) In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; (3) In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion; and (4) As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Off Label Uses

Anemia in patients with Myelodysplastic Syndrome (MDS) Have been used for the treatment of anemia in patients with MDS. [20]

Drug Name: Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx)

Indications

Anemia Due to Chronic Kidney Disease Indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.

Anemia Due to Zidovudine in HIV-infected Patients Indicated for the treatment of anemia

due to zidovudine administered at less than or equal to 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL.

Anemia in Cancer Patients on Chemotherapy Indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and upon initiation, there is a minimum of 2 additional months of planned chemotherapy. Limitations of Use: Epogen and Procrit have not been shown to improve quality of life, fatigue, or patient well-being. Epogen and Procrit are not indicated for use: (1) In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy; (2) In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; (3) In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion; (4) As a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia.

Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery Indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epogen, Retacrit, and Procrit are not indicated for patients who are willing to donate autologous blood preoperatively. Limitations of Use: Epogen and Procrit have not been shown to improve quality of life, fatigue, or patient well-being. Epogen and Procrit are not indicated for use: (1) In patients scheduled for surgery who are willing to donate autologous blood; (2) In patients undergoing cardiac or vascular surgery.

Off Label Uses

Anemia associated with HIV infection Have been used for the treatment of anemia associated with HIV infection in patients not receiving zidovudine. [5]

Anemia in Hepatitis C virus (HCV) infected patients due to combination therapy of ribavirin and interferon or peg-interferon Have been used for the treatment of anemia in patients with hepatitis C virus (HCV) infection who are being treated with the combination of ribavirin and interferon or peginterferon alfa. [20]

Anemia in patients with Myelodysplastic Syndrome (MDS) Have been used for the treatment of anemia in patients with MDS. [5, 20]

Drug Name: Mircera (methoxy polyethylene glycol-epoetin beta)

Indications

Anemia Due to Chronic Kidney Disease Indicated for the treatment of anemia associated with chronic kidney disease (CKD) in: (1) adult patients on dialysis and adult patients not on dialysis; (2) pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. Mircera is not indicated and is not recommended: (1) In the treatment of anemia due to cancer chemotherapy; or (2) As a substitute for RBC transfusions in patients who require immediate correction of anemia. Mircera has not been shown to improve symptoms, physical functioning or health-related quality of life.

2 . Criteria

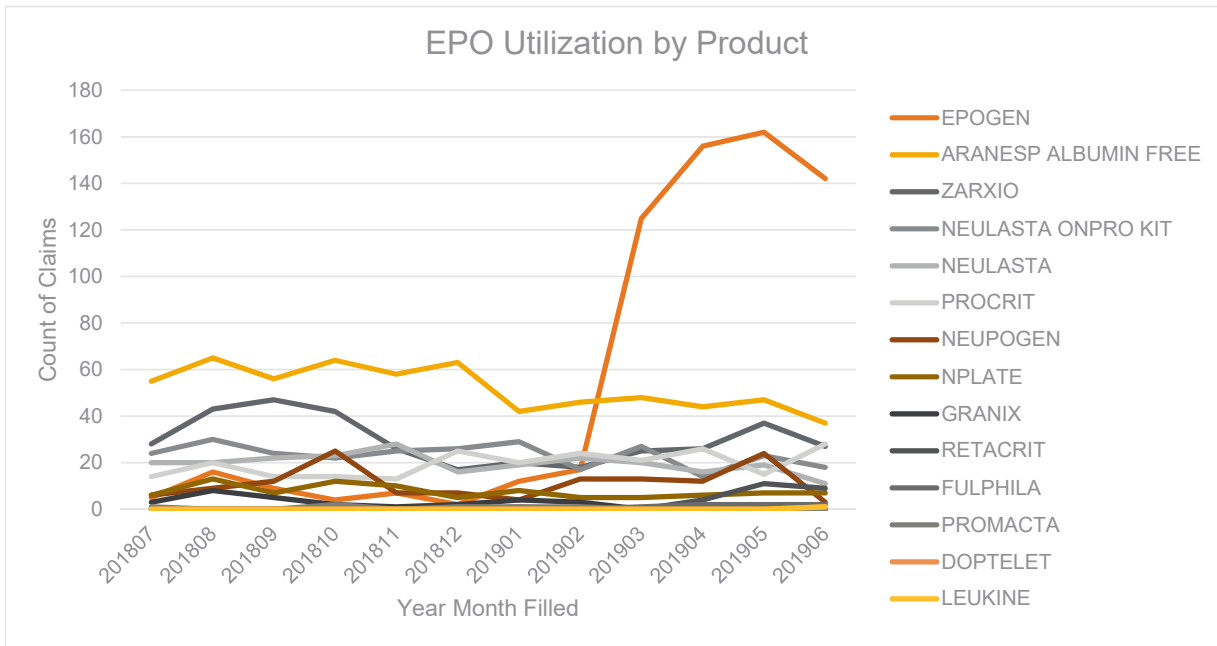
Approval Length	6 Month
Guideline Type	Prior Authorization
<p>Coverage and Limitations</p> <ol style="list-style-type: none"> 1. The recipient has been evaluated for adequate iron stores. 2. Recipients must meet one of the following criteria for coverage: <ol style="list-style-type: none"> a. Achieve and maintain hemoglobin levels within the range of 10 to 12 gm/dl in one of the following conditions: <ol style="list-style-type: none"> i. Treatment of anemia secondary to myelosuppressive anticancer chemotherapy. ii. Treatment of anemia related to zidovudine therapy in HIV-infected patients. iii. Treatment of anemia secondary to ESRD. b. Epoetin alfa (Epogen®) is indicated to reduce the need for allogenic transfusions in surgery patients when a significant blood loss is anticipated. It may be used to achieve and maintain hemoglobin levels within the range of 10 to 13 gm/dl. Darbepoetin Alfa (Aranesp®) does not have this indication. <p>Non-Covered Indications</p> <ol style="list-style-type: none"> 1. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding or bone marrow fibrosis. 2. Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML) or erythroid cancers. 3. Anemia of cancer not related to cancer treatment. 4. Any anemia associated only with radiotherapy. 5. Prophylactic use to prevent chemotherapy-induced anemia. 6. Prophylactic use to reduce tumor hypoxia. 7. Patients with erythropoietin-type resistance due to neutralizing antibodies. 8. Anemia due to cancer treatment if patients have uncontrolled hypertension. 	

Erythropoiesis Agents

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

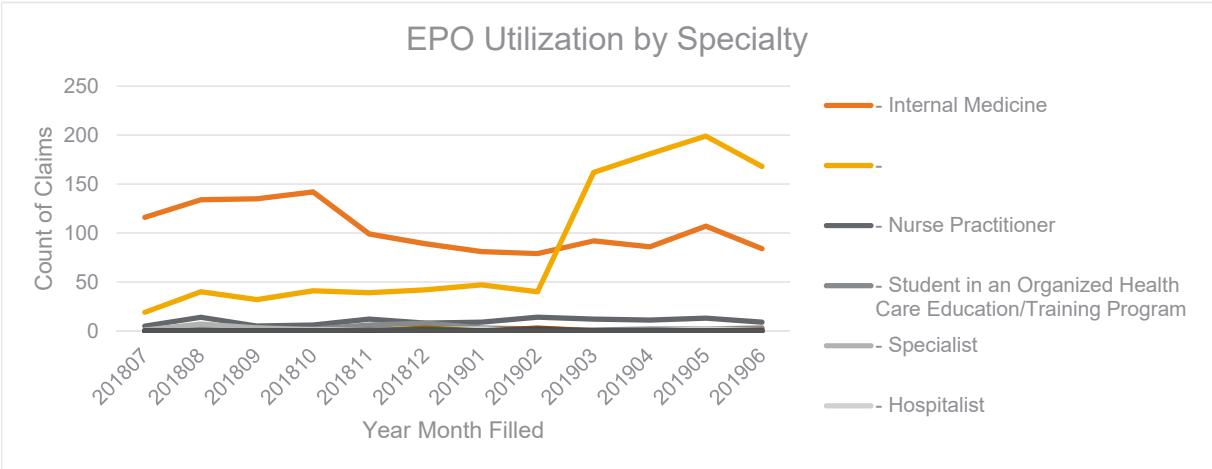
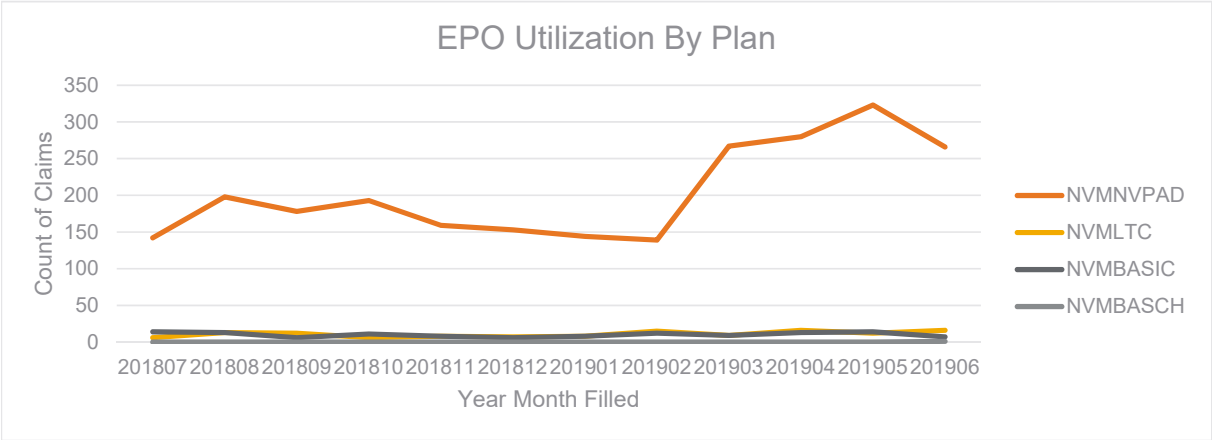
Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
EPOGEN	51	657	1372	250.17
RETACRIT	9	24	24	260
LEUKINE	1	1	14	28
ARANESP ALBUMIN FREE	150	625	857	432.82
PROMACTA	2	6	180	180
NEULASTA	78	236	236	141.6
NPLATE	11	91	91	110.44
DOPTELET	1	1	5	15
FULPHILA	5	8	28	64.2
NEUPOGEN	28	135	719	515.6
PROCRIT	45	234	906	402.87
NEULASTA ONPRO KIT	110	279	494	170.4
ZARXIO	68	356	540	815.8
GRANIX	10	29	55	70.5



Erythropoiesis Agents

July 1, 2018 - June 30, 2019

Fee for Service Medicaid



DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

H. Hematopoietic/Hematinic Agents

Therapeutic Class: Erythropoiesis Stimulating Agents (ESAs)

Last Reviewed by the DUR Board: January 24, 2008

This policy applies in all settings with the exception of inpatient facilities. Hematopoietics and Hematinics 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

Recipients must meet one of the following criteria for coverage:

- a. Achieve and maintain hemoglobin levels within the range of 10 to 12 gm/dl in one of the following conditions:
 1. Treatment of anemia secondary to myelosuppressive anticancer chemotherapy.
 2. Treatment of anemia related to zidovudine therapy in HIV-infected patients.
 3. Treatment of anemia secondary to ESRD.
- b. Epoetin alfa (Epogen®) is indicated to reduce the need for allogenic transfusions in surgery patients when a significant blood loss is anticipated. It may be used to achieve and maintain hemoglobin levels within the range of 10 to 13 gm/dl. Darbepoetin Alfa (Aranesp®) does not have this indication.

2. Non-Covered Indications

- a. Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding or bone marrow fibrosis.
- b. Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML) or erythroid cancers.
- c. Anemia of cancer not related to cancer treatment.
- d. Any anemia associated only with radiotherapy.
- e. Prophylactic use to prevent chemotherapy-induced anemia.
- f. Prophylactic use to reduce tumor hypoxia.
- g. Patients with erythropoietin-type resistance due to neutralizing antibodies.

DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

h. Anemia due to cancer treatment if patients have uncontrolled hypertension.

3. Prior Authorization Guidelines

Prior approval will be given for a one month period. Recent laboratory results are required for prior authorization, i.e. serum hemoglobin within seven days of prior authorization request.

Prior Authorization forms are available at:

<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview

Erythropoiesis Stimulating Agents

INTRODUCTION

- Iron deficiency anemia is the most common form of anemia. Anemia is also associated with a variety of conditions including cancer, chronic kidney disease (CKD), rheumatoid arthritis, human immunodeficiency virus (HIV), chronic heart failure, and chronic obstructive pulmonary disease (Schrier and Camaschella 2018, Schrier 2018).
- Management of anemia of chronic disease is often more complex, and administration of erythropoiesis-stimulating agents (ESAs) or red blood cell (RBC) transfusions may be necessary for patients with severe, symptomatic anemia (eg, hemoglobin [Hb] <10 g/dL) (Schrier and Camaschella 2018).
- Although allogeneic RBC transfusions provide rapid correction of Hb stores, they are also accompanied by significant risks, which include transmission of communicable diseases, allergic and immune transfusion reactions, volume overload, hyperkalemia, and iron overload (Carson and Kleinman 2019).
- Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow. Erythrocytes, or RBCs, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen (Hörl 2013).
- The ESAs were first introduced in the early 1980's to provide a treatment option for anemia in patients with CKD, and later, in patients with malignancies who were unable to maintain their Hb within the acceptable ranges (Schrier et al 2018).
- Although ESAs may decrease the need for RBC transfusions, multiple meta-analyses of randomized controlled trials (RCTs) have demonstrated an increase in mortality, cardiovascular events, and cancer progression without significant improvements in morbidity or quality of life (QoL) for patients receiving therapy (Collister et al 2016, Grant et al 2013, Palmer et al 2014a, Tonia et al 2012).
- The ESAs approved by the Food and Drug Administration (FDA) in the United States include Epogen (epoetin alfa), Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene glycol-epoetin beta). Retacrit is the first and only FDA-approved ESA biosimilar in the United States.
- Epoetin alfa and darbepoetin alfa products carry boxed warnings regarding shortened survival and increased risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Furthermore, the warnings emphasize to use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Medispan Therapeutic Class: Erythropoietins

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar Availability
Aranesp (darbepoetin alfa)	Amgen	09/17/2001	-
Epogen, Procrit (epoetin alfa)	Amgen	06/01/1989	+
Retacrit (epoetin alfa-epbx)*	Hospira/Pfizer	05/15/2018	-
Mircera (methoxy polyethylene glycol-epoetin beta)	Galenica	11/14/2007	-

*Retacrit is an ESA biosimilar to Epogen/Procrit.

(DRUGS@FDA 2019, Purple Book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aranesp (darbepoetin alfa) [†]	Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx) [‡]	Mircera (methoxy polyethylene-epoetin beta) [§]
Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis	✓ †	✓ *	✓
Treatment of anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA			✓
Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy	✓	✓	
Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus (HIV)-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL		✓	
Reduce the need for allogeneic red blood cell transfusions among patients with perioperative Hb > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery		✓	

*To decrease the need for transfusions in these patients.

† The safety and effectiveness of Aranesp was studied in pediatric patients 1 month to 16 years old who have CKD and are receiving or not receiving dialysis; safety and efficacy of Aranesp in pediatric patients with cancer have not been established.

‡ Indicated in pediatric patients 1 month to 16 years of age for treatment of anemia in CKD requiring dialysis, and in patients 5 to 18 years of age for treatment of anemia due to concomitant myelosuppressive chemotherapy. Limited data are available on the use of epoetin in children with HIV receiving zidovudine.

§Mircera is indicated for the treatment of anemia due to CKD in patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA

• Limitations of use:

- All ESAs have not been shown to improve QoL, fatigue, or patient well-being.
- ESAs are not indicated as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Aranesp, Epogen, Procrit, and Retacrit are not indicated for use:
 - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
 - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
 - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- Epogen, Procrit, and Retacrit are not indicated for use:
 - In patients scheduled for surgery who are willing to donate autologous blood.
 - In patients undergoing cardiac or vascular surgery.
- Mircera is not indicated for use:

Data as of February 12, 2019 JA-U/JZ-U/ALS

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- In the treatment of anemia due to cancer chemotherapy.

(Prescribing information: Aranesp 2019, Epogen 2018, Mircera 2018, Procrit 2018, Retacrit 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

- Only a few clinical studies have compared the efficacy and safety of epoetin alfa to darbepoetin alfa for the treatment of anemia due to CKD or myelosuppressive chemotherapy. None of these agents have been shown to improve QoL, fatigue, or patient well-being. Since initial FDA-approval, the ESAs have been shown to increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Earlier studies utilized ESA to maintain higher Hb targets than the targets recommended currently. Numerous observational, non-interventional, retrospective, and single-center studies have evaluated these agents in the correction of anemia due to CKD or myelosuppressive chemotherapy. However, these studies are not included in this review.
- Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). The approval of Retacrit was based on a review of evidence including extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data demonstrating its biosimilarity. Retacrit was approved as a biosimilar, not as an interchangeable product.

Anemia in CKD

- ESAs provided an attractive solution to decreasing the number of allogeneic blood transfusions; however, multiple meta-analyses of RCTs have demonstrated an increase in mortality, cardiovascular events, and cancer progression without improvement in morbidity or QoL for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a*).
- According to a Cochrane review, use of ESAs in predialysis patients corrected anemia and avoided blood transfusions compared to placebo or no treatment (*Cody et al 2016*). A total of 19 studies (N = 993) evaluated ESAs, with the majority of the studies being published prior to 2000. ESAs improved Hb (mean difference [MD] 1.90 g/dL, 95% CI, -2.34 to -1.47) and decreased the number of patients with blood transfusions (risk ratio [RR] 0.32, 95% confidence interval [CI], 0.12 to 0.83). No differences with the measure of kidney disease progression were observed. Endpoints of QoL and change in exercise capacity were not measured in a manner which was suitable for analysis.
- The harms of high Hb targets compared to lower Hb targets were evaluated. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) trial was a notable trial that found that patients with CKD with a higher target Hb had higher risk for the composite outcome of death, nonfatal myocardial infarction, stroke, and hospitalization for congestive heart failure (CHF) than patients with a lower Hb target (17.5 vs 13.5%; hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74; p = 0.03) (*Singh et al 2006*). Analysis of study data in the intent-to-treat (ITT) population and including all events from randomization until study termination or 30 days after the last dose showed a higher incidence of events in the high-Hb group (HR, 1.3; 95% CI, 1.01 to 1.62; p = 0.04). Even though the trial was halted early, evidence suggested that higher Hb levels led to an increased rate of adverse events. The prescribing information and warnings for all drugs of this class were updated to reflect these findings. Findings were similar to the Normal Hematocrit Study performed in patients with CKD on dialysis with CHF or ischemic heart disease (*Besarab et al 1998*).
- A systematic review evaluated 9 trials comparing epoetin alfa and darbepoetin alfa for all-cause mortality in patients with anemia in adults with CKD including those on dialysis (N = 2024). Duration of the trials was 20 to 52 weeks. No significant difference in mortality between epoetin and darbepoetin was detected (odds ratio [OR] 1.33; 95% CI, 0.88 to 2.01) (*Wilhelm-Leen et al 2015*).
- Numerous trials have evaluated extended dosing intervals of epoetin for patients with CKD. In general, larger doses given less frequently demonstrated similar outcomes with epoetin alfa and darbepoetin (*Benz et al 2007, Patel et al 2012, Pergola et al 2009, Pergola et al 2010, Provenzano et al 2004, Provenzano et al 2005, Spinowitz et al 2008a, Warady et al 2018*). A systematic review confirmed that various dosing frequencies of darbepoetin and epoetin result in similar mean final Hb values in patients receiving hemodialysis (*Hahn et al 2014*). Many of these dosing regimen studies

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were completed in small patient populations and open-label design. The FDA-approved dosing regimen for epoetin alfa is 3 times weekly for patients with CKD.

- Patients with CKD on dialysis should receive intravenous (IV) darbepoetin and epoetin alfa. Cases of pure red cell aplasia and severe anemia have been reported more frequently with the subcutaneous (SC) administration of ESAs in patients with CKD. Comparisons of the method of administration (IV vs SC) have been completed with epoetin and darbepoetin. In an open-label, German study, switching patients on dialysis from SC darbepoetin to IV administration led to stable mean Hb levels and mean weekly darbepoetin doses (*Bommer et al 2008*). Another open-label study showed that switching patients on dialysis from SC epoetin to IV darbepoetin resulted in stable mean Hb levels at stable darbepoetin doses after 3 months (*Chazot et al 2009*). Mircera is indicated for IV or SC administration.
- In a double-blind, multicenter, placebo-controlled, randomized clinical trial, the safety of darbepoetin in patients with type 2 diabetes mellitus, CKD, and anemia were evaluated (*Pfeffer et al 2009*). The patients had a baseline Hb level of ≤ 11 g/dL. The primary endpoint of the TREAT study was the composite of death or a non-fatal cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke or hospitalization for myocardial ischemia) and death or end-stage renal disease. The primary cardiovascular composite outcome of death or nonfatal cardiovascular event occurred in 632 patients (31.4%) of the darbepoetin group and 602 patients (29.7%) treated with placebo (HR for darbepoetin vs placebo, 1.05; 95% CI, 0.94 to 1.17; $p = 0.41$). For the individual endpoints contributing to the composite, there were no statistically significant differences between the groups for any parameter except for fatal and non-fatal stroke which occurred more frequently with darbepoetin (5% vs 2.6%; HR, 1.92; 95% CI, 1.38 to 2.68; $p < 0.001$). For the composite endpoint of death or end-stage renal disease, no significant difference was detected (darbepoetin 32.4% vs 30.5% placebo; HR, 1.06; 95% CI, 0.95 to 1.19; $p = 0.29$). The study was performed from 2004 to 2007, when the standard of care target Hb level was 13 g/dL. Additional notification was sent to investigators and participants of the adverse outcomes with higher Hb targets; however, the study protocol was not modified. A third party vendor assayed Hb levels and reported the dosage adjustment necessary for patients receiving darbepoetin. At baseline, the darbepoetin group had a lower proportion of patients with a history of CHF (31.5 vs 35.2%; unadjusted $p = 0.01$). In summary, darbepoetin in patients with anemia, diabetes and chronic renal disease did not increase the risk of the composite outcome of death or cardiovascular outcome and death or end-stage renal disease. It was noted that stroke, fatal or non-fatal, occurred more frequently in patients who received darbepoetin compared to placebo.
- A systematic review evaluated darbepoetin and the other ESAs in 21 studies in patients with CKD for the effect on blood transfusion (*Palmer et al 2014b*). Darbepoetin reduced the need for blood transfusions compared to placebo or no treatment; however, in 3 studies comparing darbepoetin to epoetin, darbepoetin had uncertain effects on RBC transfusions and all-cause mortality compared to epoetin. Darbepoetin and methoxy polyethylene glycol-epoetin beta were similar for risk of RBC transfusions.
- A Cochrane review compared the efficacy and safety of the ESAs (Mircera, epoetin alfa, epoetin beta, darbepoetin alfa, and biosimilar ESAs) in adults with CKD. A total of 56 studies ($N = 15,596$) were included in the analysis. In network analyses, there was moderate to low confidence that the ESAs prevented blood transfusions compared to placebo. The authors concluded that there was insufficient evidence to suggest superiority of any ESA formulation based on available safety and efficacy data (*Palmer et al 2014a*).
- A systematic review evaluated 17 studies ($N = 10,049$) with ESAs for effects on health-related quality of life (HRQoL) in CKD patients (*Collister et al 2016*). Higher Hb target levels (range: 10.2 to 13.6 g/dL) resulted in no statistically significant improvements in Short-Form 36 (SF-36) domains or for the Kidney Disease Questionnaire (KDQ) compared to patients on placebo or lower Hb target levels (range: 7.4 to 12 g/dL). For the KDQ, patients with higher Hb targets had an improvement of 0.5 (95% CI, -2.2 to 1.2) points in the physical symptom domain, 0.5 point improvement in the fatigue domain (95% CI, -1.6 to 0.5), and 0.2 point improvement in the depression domain (95% CI, -1.1 to 0.8). A clinically meaningful benefit is considered a minimum of 0.5 point improvement on the KDQ. The systematic review is consistent with the prescribing information and previously published reports.
- Very few randomized controlled studies comparing darbepoetin and epoetin alfa have been published. Two non-inferiority studies comparing epoetin alfa to darbepoetin alfa in the treatment of anemia of CKD demonstrated no difference in efficacy between the 2 agents. In a study of adult patients with CKD by *Nissenson et al*, the mean changes in Hb levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0 to 0.06 g/dL) groups (difference, 0.16 g/dL; 95% CI, -0.06 to 0.38; p value not reported). In a second study by *Vanrenterghem et al* ($N = 522$) of patients with CKD on dialysis, the mean change in Hb was 0.05 g/dL in the

darbepoetin alfa group compared to 0 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; p values not reported). No statistically significant differences in the mean change in Hb levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles, and no antibodies detected to either treatment (*Nissenson et al 2002, Vanrenterghem et al 2002*). An open-label trial comparing darbepoetin SC 0.45 mcg/kg once weekly and epoetin SC 50 units/kg twice weekly found similar efficacy in achieving a Hb response and similar safety profile in 166 patients with CKD not on dialysis (*Locatelli et al 2001*).

- The safety and efficacy of Mircera were established in Phase 3, multicenter, open-label, active-controlled trials that randomized patients with CKD with anemia to treatment with either Mircera or a comparator ESA.
- Four of the clinical trials assessed Mircera in the maintenance of Hb levels among patients currently treated with other ESAs for anemia of CKD (*Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007*). Patients were randomized to receive Mircera administered either once every 2 weeks or once every 4 weeks, or to continue their current ESA schedule and dose. Throughout the trials, treatment with Mircera consistently maintained Hb concentrations within the targeted range (10 to 13.5 g/dL) and demonstrated non-inferiority compared to other ESAs.
- In addition, an extension trial was conducted that demonstrated the long-term safety and efficacy of Mircera administered every 4 weeks in maintaining stable Hb levels in patients with CKD not on dialysis following correction with Mircera administered every 2 weeks (*Kessler et al 2010*).
- Other direct-comparative trials have been conducted to evaluate the safety and efficacy of Mircera to other ESAs. In the trials, mean Hb concentrations remained constant within the recommended target range in all treatment groups and further confirmed the efficacy and safety of once monthly Mircera for correction and maintenance of Hb (*Al-Ali et al 2015, Carrera et al 2010, Roger et al 2011*).
 - The PATRONUS study evaluated Mircera IV every 4 weeks to IV darbepoetin alfa every 4 weeks in patients on hemodialysis (N = 490) (*Carrera et al 2010*). For the primary endpoint, Hb response rate (average Hb \geq 10.5 g/dL with a decrease from baseline of \leq 1 g/dL) was significantly higher in patients on Mircera (64.1%) in comparison to those given IV darbepoetin alfa (40.4%) (p < 0.0001).
- A systematic review compared the efficacy and tolerability of Mircera with darbepoetin alfa for the treatment of anemia in non-dialysis dependent patients (N = 1155) with CKD (*Alsaimy et al 2014*). Based on the analysis, changes in Hb level from baseline demonstrated that Mircera was clinically non-inferior to darbepoetin alfa.
- Two studies evaluated Mircera in the correction of Hb levels in anemic patients with CKD who were not treated with an ESA at baseline.
 - In the ARCTOS study, patients (N = 324) not currently receiving dialysis were randomized to Mircera administered every 2 weeks or darbepoetin alfa administered once a week for 28 weeks. Hb response rate, defined as an increase \geq 1 g/dL vs baseline and a concentration \geq 11 g/dL, was achieved in 97.5% of patients treated with Mircera and 96.3% of patients treated with darbepoetin alfa (*Macdougall et al 2008*).
 - In the second study, patients who were receiving either peritoneal dialysis or hemodialysis were randomized to Mircera IV every 2 weeks or epoetin alfa or beta IV administered 3 times weekly for 24 weeks. Hb response rate was achieved in 93.3% of patients treated with Mircera and 91.3% of patients treated with epoetin (*Klinger et al 2007*). Peak Hb levels were 12.28 g/dL for Mircera and 12.19 g/dL for epoetin.
- A Cochrane systematic review and meta-analysis evaluated the effect of treatment with continuous erythropoiesis receptor activator (Mircera) on health outcomes from 27 RCTs in 5410 adults with anemia and CKD, vs a different ESA (darbepoetin alfa or epoetin alfa or beta) or placebo (*Sagliimbene et al 2017*).
 - The analysis demonstrated that overall, there was low certainty evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) vs epoetin alfa/beta or darbepoetin alfa respectively.
 - There was insufficient evidence to compare the effect of Mircera to placebo on clinical outcomes.
 - No studies reported comparative treatment effects of different ESAs on HRQoL.
- A systematic review and meta-analysis of 30 randomized controlled trials in adults with CKD did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (RR 2.18, 95% CI 1.31 to 3.62) (*Amato et al 2018*).

Anemia associated with chemotherapy

- In patients with anemia due to chemotherapy, ESAs should be avoided when the anticipated outcome of chemotherapy is cure. The use of ESAs for anemia from myelosuppressive chemotherapy should be at the lowest dose to avoid RBC transfusions and should be discontinued upon the completion of chemotherapy.
- The Agency for Healthcare Research and Quality (AHRQ) performed an updated meta-analysis of 59 randomized controlled studies, 5 of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to transfusion risk (pooled relative risk [RR], 1.14; 95% CI, 0.82 to 1.59; $I^2=43%$; 5 trials; N = 2005), on-study mortality (pooled HR, 0.9; 95% CI, 0.67 to 1.2; $I^2 = 72%$; 2 trials; N = 1567) and thromboembolic events (pooled RR, 0.86; 95% CI, 0.61 to 1.21; $I^2 = 0%$; 3 trials; N = 1873). ESA therapy was associated with higher thromboembolic event rates (pooled RR, 1.51; 95% CI, 1.3 to 1.74; $I^2 = 0%$; 37 trials; N = 12,570) and rates of on-study mortality (pooled HR, 1.17; 95% CI, 1.04 to 1.31; $I^2 = 0%$; 37 trials; N = 11,266) compared to controls. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa compared to control on HRQoL, tumor response and progression, overall survival or adverse outcomes (*Grant et al 2013*).
- In another systematic review, ESAs were associated with a hematological response (defined as ≥ 2 g/dL increase in Hb or $\geq 6%$ increase in hematocrit) compared to control (risk ratio, 3.39; 95% CI, 3.1 to 3.71; 31 trials; N = 6413). However, there was significant heterogeneity between trials ($I^2 = 53%$). It was noted that all trials indicated a beneficial effect of ESAs on hematological response (*Tonia et al 2012*). Other meta-analyses have reported similar findings (*Bohlius et al 2009*).
- In a patient-level meta-analysis, the effectiveness of darbepoetin in improving Hb levels and blood transfusions was evaluated in patients with chemotherapy-induced anemia with an initial Hb of ≤ 10 g/dL (*Pirker et al 2016*). Patient level data were obtained from 4, Phase 3, randomized, double-blind, placebo-controlled trials of darbepoetin of 12 to 18 weeks in duration; for this analysis, data were extracted for patients with baseline Hb ≤ 10 g/dL (n = 261 for darbepoetin; n = 273 for placebo). This represented only 33% of the enrolled population. A second analysis evaluated darbepoetin only and identified 15 studies (n = 3768) without front loading and 6 studies with front loading (n = 901). For the endpoint of Hb increase of ≥ 1 g/dL or ≥ 2 g/dL vs placebo, darbepoetin improved Hb levels (HR 2.07, 95% CI, 1.62 to 2.63) and (HR 2.91, 95% CI, 2.09 to 4.06), respectively. Mean time to ≥ 1 g/dL increase in Hb was 43 days (95% CI, 37 to 50 days) for darbepoetin and not evaluable for placebo. Median time to a ≥ 2 g/dL increase was 78 days (95% CI, 71–not evaluable days) for darbepoetin and not evaluable for placebo. Transfusions were more commonly required between the start of week 5 and end of week 12 in patients who received placebo than in patients who received darbepoetin. Note that only Amgen sponsored studies were included in this analysis, and Amgen supported the meta-analysis.
- In an open-label, multicenter, randomized noninferiority trial, the impact on epoetin 40,000 units weekly on tumor outcomes was compared with the best supportive care for the treatment of anemia in 2098 patients receiving chemotherapy for metastatic breast cancer (*Leyland-Jones et al 2016*). The median progression-free survival (PFS) (based on investigator-determined disease progression) was 7.4 months in both groups (HR 1.089, 95% CI, 0.988 to 1.200) with the upper bound exceeding the prespecified noninferiority margin of 1.15. There was a reduction in the number of RBC transfusions in the epoetin-treated patients vs best supportive care (5.8 vs 11.4%; $p < 0.001$), while the rate of thrombotic vascular events was higher (2.8 vs 1.4%, respectively; $p = 0.038$). Overall, the noninferiority of treatment with epoetin was not established, and RBC transfusion was shown to be the best approach to manage anemia in patients with metastatic breast cancer receiving chemotherapy.
- Extended dosing intervals have been investigated. These extended dosing intervals of epoetin such as once every 3 weeks are not FDA-approved (*Glasy et al 2009*).

Anemia associated with zidovudine in patients with HIV

- Early trials with epoetin in HIV were performed when zidovudine was one of only a few antiretrovirals available for treatment of HIV. Since the late 1980's and 1990's, numerous antiretroviral treatment options have become available and resulted in limited use of zidovudine. A meta-analysis of 4, small, double-blind, randomized trials evaluated the efficacy and safety of epoetin compared to placebo in improving hematocrit values in patients with HIV or Acquired Immunodeficiency Syndrome (AIDS) (*Henry et al 1992*). In the 12-week trials, epoetin significantly increased hematocrit

from baseline compared to placebo in patients with an endogenous erythropoietin level of ≤ 500 IU/L (mean change, 4.6 vs 0.5, respectively; $p = 0.0002$; mean difference, 3.9; 95% CI, 1.8 to 6).

- A meta-analysis of 6 randomized, clinical trials with 537 subjects evaluated the risk of death associated with epoetin or placebo in patients with HIV or AIDS and anemia (*Martí-Carvajal et al 2011*). None of the studies included evaluated death as a primary outcome. The risk of death was not statistically significant for epoetin versus placebo or when comparing epoetin once weekly vs 3 times weekly. Studies had significant attrition bias.

Reduced need for transfusions associated with surgery

- Clinical trials have evaluated the use of epoetin in reducing the need for blood transfusions in adults undergoing elective surgeries (*de Andrade et al 1996, Faris et al 1996, Goldberg et al 1996, Zhao et al 2016*). Epoetin is associated with an increased risk of deep venous thrombosis; therefore, appropriate preventative measures should be utilized.
- In a double-blind, multicenter, placebo-controlled trial, the efficacy and safety of epoetin 300 units/kg and 100 units/kg were compared to placebo in 316 adult patients scheduled for elective orthopedic surgery. The primary outcome was the rate of transfusion which was significantly lower in patients receiving epoetin 300 units/kg with a pretreatment Hb of >10 to ≤ 13 g/dL (epoetin 300 units/kg, 16%; epoetin 100 units/kg, 23%; placebo, 45%; $p = 0.024$) (*de Andrade et al 1996*).
- Epoetin has been shown to reduce the need for blood transfusions in 200 patients undergoing elective orthopedic surgeries compared to placebo (*Faris et al 1996*). Epoetin 100 units/kg/day (17%) and epoetin 300 units/kg/day (25%) led to a reduction in the percentage of patients who required a blood transfusion following a major elective orthopedic surgery compared to control (54%; $p \leq 0.001$ for both epoetin groups vs placebo). There was no significant difference between the 2 epoetin groups (p value not reported). The mean number of units transfused for each patient was significantly lower in the epoetin groups compared to the placebo group (epoetin 100 units/kg/day, 0.37 ± 0.96 ; epoetin 300 units/kg/day, 0.58 ± 1.15 ; placebo, 1.42 ± 1.67 ; $p < 0.01$ for both epoetin groups compared to placebo). There was no significant difference between the epoetin groups ($p > 0.05$).
- A meta-analysis evaluated 7 studies ($N = 2439$) to evaluate efficacy and safety of treatment with erythropoietin compared with controls (placebo or no intervention) in patients undergoing total hip or knee arthroplasty (*Voorn et al 2016*). Erythropoietin was shown to reduce exposure to RBC transfusion in both hip (RR 0.45, 95% CI, 0.33 to 0.61) and knee (RR 0.38, 95% CI 0.27 to 0.53) arthroplasty, without differences between indications ($p = 0.44$), and the mean number of transfused RBC units was decreased in erythropoietin-treated patients (mean difference -0.57, 95% CI -0.86 to -0.29) for both indications. There were no differences detected in thromboembolic and vascular adverse events (RR 1.14, 95% CI 0.71 to 1.84), nor other adverse events (RR 1.01, 95% CI 0.94 to 1.01) between erythropoietin compared with controls.
- A systematic review and meta-analysis evaluated 15 RCTs ($N = 2155$) to evaluate the hematopoiesis-promoting effect and potential complications, preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty (*Zhao et al 2016*). Preoperative use of erythropoietin was associated with lower exposure to allogeneic blood transfusion (OR = 0.41) and higher hemoglobin concentration after surgery (standardized mean difference 0.86; $p < 0.001$). Complications were not generally reported, but there was no significant difference between the group with and without erythropoietin based on given data.

CLINICAL GUIDELINES

CKD

- The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In all adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The guidelines recommend that 'copy' versions of ESAs should only be those which have been designated true biosimilars (*KDIGO 2012*).
- Based on the recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF – KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in CKD, the Hb level at which ESA therapy should be initiated as well as the Hb target during therapy should be based on the individual patient, potential benefits (including improvement in QoL and avoidance of transfusion) and potential harms of therapy (including the risk of life-threatening adverse events). Generally speaking, the guidelines recommend that patients with CKD, both dialysis and nondialysis, receiving ESA therapy have a Hb target range of 11 to 12 g/dL, and the Hb levels should not exceed 13 g/dL. This recommendation is based on clinical studies demonstrating that patients with a Hb ≥ 13 g/dL do not

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have improvements in survival, hospitalization or left ventricular hypertrophy and may in fact be more prone to excessive adverse cardiovascular events compared to individuals with lower Hb targets (*KDOQI 2006, KDOQI 2007*).

- In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of CKD resulting from data showing that using ESAs to target a Hb level of >11 g/dL increased the risk of cardiovascular events, without providing any additional benefit to patients (*FDA Drug Safety Communication 2011*). For patients with anemia of CKD who are not on dialysis, ESA treatment can be considered when the Hb level is <10 g/dL, and the dose should be reduced or interrupted when Hb exceeds 10 g/dL. For patients with anemia of CKD currently on dialysis, ESA treatment should be initiated when the Hb level is <10 g/dL and the dose should be reduced or interrupted when Hb approaches or exceeds 11 g/dL.
- The KDOQI US Commentary on the 2012 KDIGO guidelines state KDOQI continues to endorse the FDA-recommended upper cutoff of 11 g/dL (*Kliger et al 2013*).
- The European Renal Best Practice guidelines state Hb target range in patients with CKD should be 11 to 12 g/dL, ESAs should not be used to maintain Hb above 11.5 g/dL, and Hb should not exceed 13 g/dL (*Locatelli et al 2009, Locatelli et al 2010, Locatelli et al 2013*). Continuous erythropoiesis receptor activator (Mircera), a modified recombinant human erythropoietin, has a considerably longer half-life than other ESAs and should be dosed once every 2 weeks for anemic correction and once every 4 weeks for maintenance of Hb levels. The safety and tolerability of continuous erythropoiesis receptor activator are similar to that of other ESAs. Biosimilars of epoetin alfa can only be administered intravenously and should not be used in exchange of the original ESA or other ESAs without physician's approval. A lower Hb target range of 10 to 12 g/dL is reasonable in nondialysis patients with type 2 diabetes. In initiating and maintaining ESA therapy, the potential benefits of reducing blood transfusions and anemia-related symptoms should be balanced against the risks of harm in individual patients (eg, stroke, vascular access loss, or hypertension). ESAs should be used with great caution, if at all, in CKD patients with active malignancy, in particular when cure is the anticipated outcome, or with a history of stroke or malignancy. The lowest possible ESA dose should be used to reach the Hb target.

Chemotherapy Associated Anemia

- Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).

Perioperative Use of ESA

- Literature supports the use of ESAs with or without iron, as ESAs are effective in reducing the number of patients requiring allogeneic blood transfusions and reducing the volume of allogenic blood transfused (*American Society of Anesthesiologists Task Force 2015*) (Category A1-B evidence – supported by a sufficient number of randomized clinical trials to conduct a meta-analysis and supported by membership opinion).
 - Insufficient evidence exists to evaluate the efficacy of ESA with iron compared to ESA without iron.
 - ESAs with or without iron may be given, when possible, to reduce the need for allogeneic blood transfusions in selected patient populations such as renal insufficiency, anemia of chronic disease, or cases of refusal of transfusion.

SAFETY SUMMARY

- **Contraindications:**
 - Epoetin alfa from multiple-dose vials contains benzyl alcohol and is contraindicated for use in neonates, infants, pregnant women, and lactating women.
 - Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients.
 - When therapy is needed in neonates and infants, or pregnant or nursing mothers, use single-dose vials.
 - ESAs should not be used in patients with uncontrolled hypertension.
 - ESAs are contraindicated if pure red blood cell aplasia (PRCA) begins after treatment with erythropoietin agents.
- **Boxed Warnings:**
 - ESAs increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
 - In controlled trials, patients with CKD experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to a target Hb level of > 11 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks. Use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.

- In patients with cancer, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. The warnings emphasize to only administer darbepoetin, epoetin, or epoetin alfa-epbx for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Mircerca is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircerca was terminated early because of more deaths among patients receiving Mircerca than another ESA.
- Perisurgery: Deep venous thrombosis prophylaxis is recommended when epoetin alfa is used preoperatively.
- Key Warnings/Precautions:
 - ESAs increase the risk of seizures in patients with CKD.
 - Epoetin alfa contains albumin, a derivative of human blood. There is an extremely remote risk for transmission of viral diseases.
 - Severe cutaneous reactions, including erythema multiforme and Stevens-Johnson Syndrome/toxic epidermal necrolysis, have been reported in patients treated with ESAs.
 - There is a risk of serious adverse reactions due to benzyl alcohol preservative in multiple-dose vials of epoetin alfa. Do not mix epoetin alfa with bacteriostatic saline (which also contains benzyl alcohol) when administering to neonates, infants, pregnant women, and lactating women.
 - Serious and fatal reactions including “gaspings syndrome” may occur in neonates and infants treated with benzyl alcohol-preserved drugs. The “gaspings syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.
 - There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
 - The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known
 - There is a risk of PRCA with darbepoetin alfa, epoetin alfa, epoetin alfa-epbx, and methoxy polyethylene glycol-epoetin beta therapy.
 - ESAs may decrease progression-free survival and overall survival in patients with breast cancer, lymphoid malignancy, cervical cancer, advanced head and neck cancer, non-small cell lung cancer or other malignancies.
- Risk Evaluation and Mitigation Strategy (REMS):
 - On April 13, 2017, the FDA removed the REMS from Aranesp, Epogen, and Procrit (*FDA REMS program 2019, Information for Epogen/Procrit 2017*). The decision was based on a survey showing that prescribers were already educated on the potential contribution of these products to the decreased survival or increased risk of tumor progression or recurrence when used for anemia due to myelosuppressive chemotherapy. Moreover, most data showed that ESAs were prescribed for FDA-approved indications. Due to removal of the REMS, health care providers and hospitals are no longer required to enroll and become certified to prescribe and dispense these agents.
- Adverse events
 - The most commonly reported adverse events with ESAs include hypertension, arthralgia, muscle spasm, and fever.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aranesp (darbepoetin alfa)	Single-dose vials, single-dose prefilled syringe	IV or SC injection	<p>Anemia associated with CKD for patients on dialysis when Hb < 10 g/dL: Initial, once weekly or once every 2 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL</p> <p>Anemia associated with CKD for patients not on dialysis when Hb is < 10 g/dL, and the rate of decline indicates a blood transfusion is likely</p>	<ul style="list-style-type: none"> ● Safety and efficacy of Aranesp in adults and pediatric patients were similar for the initial treatment of anemia in patients with CKD or in transition from another

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			<p>and reducing RBC transfusion-related risks is a goal: Initial, once every 4 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 10 g/dL.</p> <p><u>Pediatrics with CKD</u>: Initiate when Hb is < 10 g/dL.</p> <p><u>Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned</u>: Initial, once weekly or once every 3 weeks until completion of a chemotherapy course; maintenance, dose should be individualized to maintain desired response.</p>	<p>erythropoietin.</p>
<p>Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx)</p>	<p>Multiple-dose vials (preserved solution)*, single-dose vials (preservative-free solution)</p>	<p>IV or SC injection</p>	<p><u>Anemia associated with CKD, including patients on dialysis and patients not on dialysis</u>: Initial, 3 times weekly; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). For pediatric patients, 3 times weekly (dialysis).</p> <p><u>Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned</u>: Initial, 3 times weekly or once weekly until completion of a chemotherapy course; maintenance, dose should be individualized to maintain the lowest Hb level sufficient to avoid red blood cell transfusion. Pediatric patients (5 to 18 years of age): weekly until completion of chemotherapy course.</p> <p><u>Anemia associated with therapy of zidovudine in HIV-infected patients with endogenous serum erythropoietin levels < 500 mUnits/mL</u>: Initial, 3 times weekly for 8 weeks; maintenance, dose should be individualized to maintain desired response. Withhold epoetin if Hb >12 g/dL.</p> <p><u>Treatment of anemic patients (Hb > 10 to < 13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions</u>: daily dose for 10 days</p>	<ul style="list-style-type: none"> • Benzyl alcohol, found in multiple-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications, which are sometimes fatal, in premature infants. Benzyl alcohol has also been associated with serious adverse events and death, particularly in pediatric patients. • Single-dose preservative-free vials should be used in neonates and infants, as well as pregnant and nursing women.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			before surgery, on the day of surgery and for 4 days after surgery; alternative dosing schedule is once weekly, at 21, 14 and 7 days before surgery, with a fourth dose on the day of surgery.	
Mircera (methoxy polyethylene glycol-epoetin beta)	Prefilled syringes	IV or SC injection	<p><u>Anemia associated with CKD, including adult patients on dialysis and patients not on dialysis:</u> Initial, once every 2 weeks; dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis).</p> <p>Once the Hb has been stabilized, may be administered once monthly.</p> <p><u>Treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA:</u> once every 4 weeks at a dose based on the total weekly ESA dose at the time of conversion</p>	<ul style="list-style-type: none"> • Should be injected in the abdomen, arm or thigh with SC administration. • Pregnancy Category C†

*Retacrit is only available as single-dose vials.

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

See the current prescribing information for full details.

- The iron status in all patients should be evaluated in all patients before and during treatment, and iron repletion maintained. Other causes of anemia should be corrected or excluded before initiating ESA.
- IV administration of ESAs is recommended for patients receiving hemodialysis.
- For all ESAs, the dosing should be individualized and the lowest dose sufficient to reduce the need for RBC transfusions should be used.

CONCLUSION

- The FDA-approved erythropoiesis-stimulating agents (ESAs) in the United States are Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene-glycol epoetin beta). Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). All agents are indicated for the treatment of anemia associated with CKD.
 - Aranesp, Epogen, Procrit, and Retacrit are also indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy in patients with non-myeloid malignancies.
 - Epogen, Procrit, and Retacrit are also indicated for treatment of anemia related to therapy with zidovudine in HIV-infected patients as well as the treatment of anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
- Clinical trials and meta-analyses comparing the efficacy of epoetin alfa and darbepoetin alfa for the treatment of anemia associated with CKD as well as anemia due to concomitant chemotherapy have demonstrated no differences between the agents (*Bohlius et al 2009, Collister et al 2016, Grant et al 2013, Nissenon et al 2002, Palmer et al 2014a, Palmer et al 2014b, Vanrenterghem et al 2002, Tonia et al 2012, Wilhelm-Leen et al 2015*).

- A systematic review and meta-analysis did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (*Amato et al 2018*).
- Numerous RCTs provide supportive evidence demonstrating the effectiveness of Mircera for the correction and maintenance of Hb in patients with anemia of CKD. Throughout the trials, treatment with Mircera corrected and maintained Hb concentrations within the targeted Hb range and demonstrated non-inferiority compared to other ESAs (*Al-Ali et al 2015, Carrera et al 2010, Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007, Roger et al 2011*). A meta-analysis demonstrated a low certainty of evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality, major adverse cardiovascular events, or need for blood transfusion vs epoetin alfa/beta or darbepoetin alfa (*Saglimbene et al 2017*).
- The ESAs are commonly used for the treatment of anemia associated with CKD to reduce the need for transfusions. The KDIGO guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The KDOQI guidelines state that each of the agents is effective at achieving and maintaining target Hb levels, and endorse the FDA-recommended upper cutoff of 11 g/dL (*KDIGO 2012, KDOQI 2006, KDOQI 2007, Kliger et al 2013*).
 - Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).
- All ESAs carry a boxed warning of increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression.
 - Multiple-dose vials of Epogen (epoetin alfa) and Procrit (epoetin alfa) contain benzoyl alcohol.
- Aranesp (darbepoetin alfa) is administered weekly or every 2 weeks, Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) are administered 1 to 3 times weekly and Mircera (methoxy polyethylene-glycol epoetin beta) is administered every 2 to 4 weeks.

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Regranex (becaplermin)





Prior Authorization Guideline

Guideline Name Regranex (becaplermin)

1 . Indications

Drug Name: Regranex Gel (becaplermin)

Indications

Diabetic Neuropathic Ulcers Indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply, when used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control. Limitations of Use: The efficacy of Regranex Gel has not been established for the treatment of pressure ulcers and venous stasis ulcers and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers. The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. Regranex is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

2 . Criteria

Product Name: Regranex

Approval Length	5 Months
Guideline Type	Prior Authorization
Approval Criteria	
Approval will be given if all the following criteria are met and documented:	
a. Diagnosis of lower extremity diabetic ulcer(s);	
AND	
b. Recipient must be age 16 years or older.	

AND

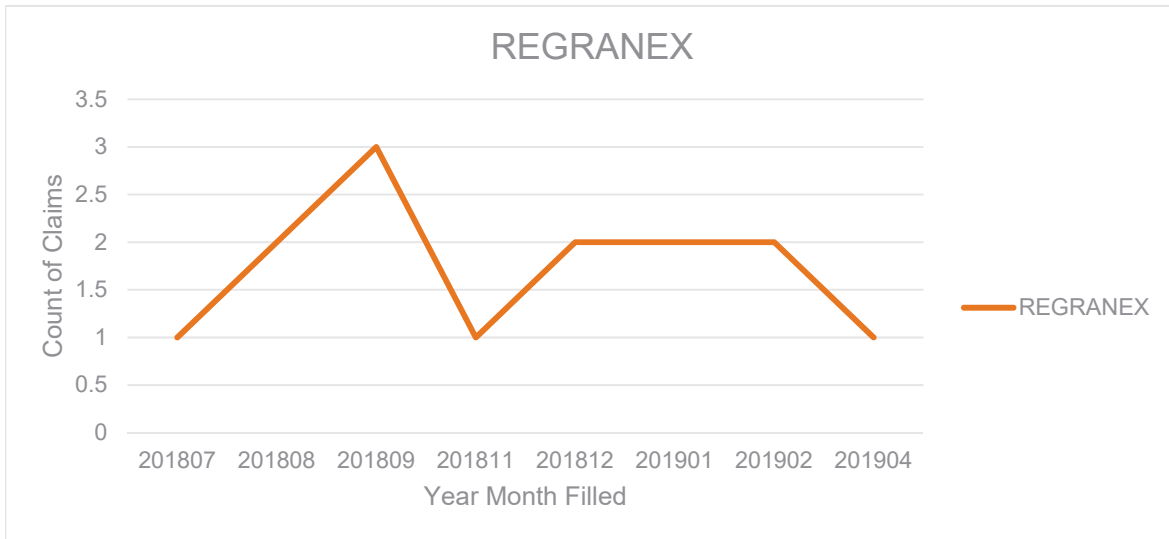
- c. Treatment will be given in combination with ulcer wound care (e.g., debridement, infection control and/or pressure relief).

Regranex Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
REGRANEX	7	14	374	210



K. Regranex®

Therapeutic Class: Diabetic Ulcer Preparations, Topical
Last Reviewed by the DUR Board: July 17, 2008

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

1. Coverage and Limitations

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

- a. Diagnosis of lower extremity diabetic ulcer(s); and
- b. Recipient must be age 16 years or older.

2. Prior Authorization Guidelines

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

Therapeutic Class Overview

Enzyme preparations and wound healing products

INTRODUCTION

- The appropriate treatment of wounds usually includes redistribution of pressure off the wound, the selection of appropriate dressings, and debridement (the removal of devitalized tissue). In addition to enzymatic debridement, other debridement options include mechanical debridement with gauze dressings, sharp surgical debridement, autolytic debridement with occlusive dressings, or application of exogenous enzymes. Treatment guidelines recommend surgical (sharp) debridement over enzymatic debridement according to the literature available (*Lipsky et al 2012, Association for the Advancement of Wound Care 2010, Stevens et al 2014*).
- Prior to a Food and Drug Administration (FDA) mandate in 2008, papain-containing products were available for the treatment of wounds. These products were withdrawn from the market due to serious safety concerns, including hypersensitivity reactions resulting in anaphylactic reactions and cardiovascular issues. After 2009, all topical papain-containing products must have FDA-approval to be manufactured or shipped (*FDA 2015*).
- This review focuses on the products that are FDA-approved for the debridement of necrotic tissue (Santyl [collagenase]) and the treatment of lower extremity diabetic ulcers (Regranex [becaplermin]). Becaplermin is a recombinant formulation of human platelet-derived growth factor.
- Medispan Therapeutic Classes: Enzymes – topical (Santyl); Wound care products (Regranex)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Regranex (becaplermin)	-
Santyl (collagenase)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Regranex (becaplermin)	Santyl (collagenase)
Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Regranex is indicated as an adjunct to, and not a substitute for, good ulcer care practices.	✓ *	
Debridement of chronic dermal ulcers and severely burned areas		✓

*Limitations of use: The efficacy of Regranex has not been established for the treatment of pressure ulcers and venous stasis ulcers. The effects of Regranex on exposed joints, tendons, ligaments, and bone have not been established in humans. Regranex is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

(*Prescribing information: Regranex 2018, Santyl 2016*)

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

CLINICAL EFFICACY SUMMARY

- A literature search produced limited data evaluating the efficacy of the enzyme prep and wound healing products included in this review. Head-to-head trials with becaplermin and other pharmacologic agents are not available.

Therapeutic Class Overview

Enzyme preparations and wound healing products

- For collagenase, 2 small head-to-head trials are available: one comparing collagenase to papain/urea ointment (which is no longer commercially available), and 1 comparing collagenase to silver sulfadiazine (SSD) ointment (*Alvarez et al 2002, Ostlie et al 2012*).
 - An open-label, multicenter, randomized clinical trial (RCT) with 28 patients evaluated collagenase ointment once daily compared to papain/urea ointment once daily (no longer commercially available) until complete debridement or 4 weeks (*Alvarez et al 2002*). The papain/urea ointment was significantly more effective in reducing the amount of non-viable, necrotic tissue at each evaluation compared to the collagenase ointment ($p < 0.0167$). Development of granulation was significantly enhanced in the papain/urea group compared to the collagenase group (P value not reported). Epithelialization generally correlated with the development of a granulating wound bed, but the increase in the amount of epithelial tissue did not predict a significantly different rate of reduction in the wound area.
 - In an open-label, single-center, RCT, 100 children with partial thickness burns were treated with initial debridement followed by SSD for 2 days (*Ostlie et al 2012*). Patients continued to receive daily debridement with either collagenase ointment plus polymyxin ($n = 50$) or SSD daily ($n = 50$). Debridement continued for 10 days or until wound healing. Grafting occurred after 10 days if the wound did not heal. The need for skin grafting did not differ between the collagenase group (32%) and the SSD group (36%) ($p = 0.68$). There were no significant differences between the collagenase and SSD groups for time to skin grafting (12.9 ± 2 vs 13.5 ± 4.6 days) or length of hospitalization (11.3 ± 5.8 vs 11.2 ± 5.2 days). Seven of 50 patients in the collagenase group and 1 of 50 patients in the SSD group experienced a burn wound infection, but this difference did not reach statistical significance ($p = 0.06$).
- There are conflicting clinical data for becaplermin regarding efficacy. Several meta-analyses have been completed with each noting the difficulty in comparing the available data due to heterogeneity and clinical trial methodological issues (*Wieman 1998, Smiell et al 1999, Perry et al 2002*).
 - A meta-analysis by Wieman described the results of 4 clinical trials ($n = 922$) of becaplermin and demonstrated a significantly higher incidence of complete healing in the patients receiving becaplermin 30 μg and/or 100 μg gel in 2 studies (only the 100 μg gel is commercially available) (*Wieman 1998*). The other 2 studies either showed no significant difference between active treatment group and placebo or good ulcer care, or were not powered to detect a difference between becaplermin and standard care. Pooled safety data for becaplermin showed that erythematous rash was more common than placebo (2 vs 1%) (*Smiell 1998*). Mortality rates did not differ between becaplermin treatment and other therapy groups.
 - In a similar analysis, the efficacy and safety of becaplermin were evaluated in the same 4 RCTs enrolling 922 patients with nonhealing, lower extremity diabetic ulcers (*Smiell et al 1999, Steed et al 1995, Wieman 1998, Wieman et al 1998, d'Hemecourt et al 1998*). Studies 1 through 3 were double-blind; however, study 4 was evaluator-blinded and compared becaplermin to good ulcer care alone. In all studies, becaplermin or placebo gel were applied once daily and kept in place for 12 hours with saline moistened gauze and then rinsed away before the second dressing change with saline moistened gauze. Becaplermin gel was administered at 30 mcg/g in studies 1 and 2 and 100 mcg/g (FDA-approved strength) for studies 3 and 4. The primary endpoint was complete healing within 20 weeks. The meta-analysis determined that patients with baseline ulcer area of $\leq 10 \text{ cm}^2$ (95% of the population) were the focus of the analysis due to homogeneity of treatment responses (*Smiell et al 1999*). The estimated probability of complete healing was significantly higher ($p = 0.007$; logistic regression model) with becaplermin 100 mcg/g gel vs placebo gel.
 - A post hoc analysis evaluated the same 4 clinical trials for efficacy rates of becaplermin on ulcer healing rates (*Perry et al 2002*). Authors suggested that the size (area) of the baseline ulcer should be taken into account when comparing the overall efficacy of becaplermin to placebo.
 - An open-label, multicenter study by Embil et al showed that complete healing of ulcers of chronic, neuropathic, lower extremity diabetic ulcers was achieved in 57.5% of patients receiving becaplermin 100 μg gel with once daily dressing changes; all patients ($n = 134$) in this study received active treatment for 20 weeks or until complete wound healing (*Embil et al 2000*).

CLINICAL GUIDELINES

- The American Diabetes Association (ADA) 2018 Diabetes standards of care recommend a foot evaluation at least annually for patients with diabetes to identify risk factors for ulcers and amputations (*ADA 2018*).
- For diabetic wound infections, the Infectious Diseases Society of America notes that sharp or surgical methods of debridement are best, and clinicians may consider growth factors as 1 of several adjunctive therapies for selected diabetic foot wounds that are slow to heal (*Lipsky et al 2012*).
- The International Diabetes Federation (IDF) recommends offloading of pressure, using various modalities such as debridement, surgery, or negative pressure wound therapy. Adjunctive therapies such as topical antimicrobials or wound dressings may also be used. For diabetic foot ulcers that fail to demonstrate improvement (> 50% wound area reduction) after ≥ 4 weeks of standard wound therapy, adjunctive therapies such as platelet-derived growth factor, living cellular therapy, extracellular matrix products, negative pressure therapy, or amniotic membrane products may be used. There are no recommendations with regard to the efficacy or effectiveness of these therapeutic options (*IDF 2017*).
- The International Working Group on the Diabetic Foot (IWGDF) guidance recommends that local wound care include debridement of the ulcer (with a scalpel), dressings to control excess exudation and maintaining a moist environment, and to consider negative pressure therapy to heal post-surgical wounds and systemic hyperbaric oxygen in poor healing wounds to hasten wound healing (*Schaper et al 2017*). Routine wound management using biologically active products such as collagen, growth factors, and bio-engineered tissue in neuropathic ulcers and the use of silver or other antimicrobial dressings are not well supported by available evidence. More specifically, the IWGDF do not recommend agents to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care (strength of recommendation: strong; level of evidence: low) (*Game et al 2016*). This includes the use of recombinant platelet-derived growth factor. Six trials have shown either no improvement in healing between the intervention and control group or there were significant methodological issues with the clinical trials.
- The Wound Healing Society updated guidelines for the management of diabetic foot ulcers in 2016. In addition to increasing oxygenation, nutrition and promotion of wound healing, several adjuvant agents are recommended for the promotion of wound healing. Topical platelet-derived growth factors reduce the time to healing and increase the proportion of ulcers that heal (Level I: meta-analyses of multiple RCTs or at least 2 RCTs supporting the intervention). Wound debridement is necessary to remove devitalized tissues, reduce bacterial burden and remove dead cells. Maintenance debridement is required to maintain the appearance and readiness of the wound. Methods of debridement include surgical, enzymatic, mechanical, biological, or autolytic; there is little evidence to support that one method is superior to another (*Lavery et al 2016*).
- The Agency for Healthcare Research and Quality (AHRQ) completed a comparative effectiveness review on pressure ulcer treatment strategies (*Saha et al 2013*). Debriding enzymes, including collagenase, had insufficient evidence about their effectiveness due to the differences in the enzymes studied and the outcomes measured. No recommendation regarding collagenase was included.
- The American College of Physicians released guidelines in 2015 for the treatment of pressure ulcers. Clinicians should use protein or amino acid supplementation in patients with pressure ulcers to reduce wound size (Grade: weak recommendation, low-quality evidence). Hydrocolloid or foam dressings are useful in patients with pressure ulcers (Grade: weak recommendation, low-quality evidence). Use of electrical stimulation in addition to standard treatment has been shown to accelerate the healing rate of stage 2 to 4 ulcers (Grade: weak recommendation, moderate-quality evidence) (*Qaseem et al 2015*).
- The Association for the Advancement of Wound Care (AAWC) 2010 guidelines recommend debridement of pressure ulcer areas with eschar and/or devitalized tissue to manage bacterial load (*AAWC 2010*). Selection of autolytic, enzymatic, mechanical, surgical, larval, or other debridement depends on the pressure ulcer status, patient's condition, and goals of care. These guidelines note that autolytic debridement is effective and possibly more effective than enzymatic debridement with collagenase. Efficacy of enzymatic debridement varies with different enzymes. Collagenase has been shown to be more effective than placebo. Growth factors are not indicated in pressure ulcers.
- Guidelines from the Infectious Diseases Society of America for the management of skin and soft tissue infections recommend surgical debridement but do not mention enzymatic debridement (*Stevens et al 2014*).

SAFETY SUMMARY

- In November 2018, the Regranex label had the boxed warning and a warning from the Warning and Precautions section for increased rate of mortality secondary to malignancy removed.
- Contraindications
 - Regranex is contraindicated in patients with known neoplasm(s) at the site(s) of application.
 - Santyl is contraindicated in patients who have shown local or systemic hypersensitivity to collagenase.
- Warnings and precautions
 - Regranex
 - If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered. Consider interruption or discontinuation and further evaluation (e.g., patch testing) as dictated by clinical circumstances.
 - Santyl
 - The optimal pH range of collagenase is 6 to 8. Higher or lower pH conditions will decrease the enzyme's activity, and appropriate precautions should be taken.
 - The enzymatic activity is also adversely affected by certain detergents, and heavy metal ions such as mercury and silver, which are used in some antiseptics.
 - Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.
 - A slight transient erythema has been noted in the surrounding tissue, particularly when Santyl Ointment was not confined to the wound.
- Adverse effects
 - Regranex
 - Erythematous rashes and burning sensations have been reported post-marketing. In trials, erythematous rashes occurred equally between patients treated with Regranex Gel and placebo (2% in each group).
 - Santyl
 - No allergic sensitivity or toxic reactions noted when used as directed. One case of systemic manifestations of hypersensitivity to collagenase was reported in a patient treated for more than 1 year with a combination of collagenase and cortisone.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Regranex (becaplermin)	Gel, 0.01%	Topical	Once daily	The amount of Regranex gel to be applied will vary depending upon the size of the ulcer area. The greatest length and width of the ulcer should be measured and a formula should be used to calculate the length of gel to apply. Spread over the entire ulcer area to yield a thin continuous layer of approximately 1/16 of an inch thickness.
Santyl (collagenase)	Ointment 250 units/gram	Topical	Once daily	Santyl may be applied directly to the wound or to a sterile gauze pad which is then applied to the wound. Use should be terminated when debridement of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				necrotic tissue is complete and granulation tissue is well established.

See the current prescribing information for full details

CONCLUSION

- One enzyme preparation agent (Santyl) and 1 wound healing product (Regranex) are FDA-approved for the debridement of necrotic tissue and treatment of diabetic neuropathic ulcers, respectively.
- The 2016 Wound Healing Society guidelines for the management of diabetic foot ulcers recommend increasing oxygenation, nutrition and promotion of wound healing (Lavery *et al* 2016). The guidelines also suggest topical platelet-derived growth factors to reduce the time to heal and increase the proportion of ulcers that heal. Wound debridement is also suggested to remove devitalized tissues, reduce bacterial burden, and remove dead cells. Methods of debridement include surgical, enzymatic, mechanical, biological, or autolytic; however, there is little evidence to support that 1 method is superior to another.
- The IWGDF guidance recommends debridement of the ulcer, wound dressings to control excess exudation, and maintaining a moist environment (Schaper *et al* 2017). Routine wound management using biologically active products such as collagen, growth factors, and bio-engineered tissue in neuropathic ulcers and the use of silver or other antimicrobial dressings are not well supported by available evidence. More specifically, the IWGDF does not recommend agents to improve wound healing by altering the biology of the wound, including growth factors including the use of recombinant platelet-derived growth factor, bioengineered skin products and gases, in preference to accepted standards of good quality care (strength of recommendation: strong; level of evidence: low) (Game *et al* 2016). Six trials have shown either no improvement in healing between the intervention and control group or there were significant methodological issues with the clinical trials.
- Regranex should be reserved for use in treating diabetic neuropathic ulcers.

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Publication Date: April 2, 2019

Topical, Local Anesthetics





Prior Authorization Guideline

Guideline Name: Lidoderm 5% Patches

1 . Indications

Drug Name: Lidoderm 5% Patches

Indications

Relief of pain associated with postherpetic neuralgia

2. Criteria

Product Name: Lidocaine 5% patch, Lidoderm

Guideline Type	Prior Authorization
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Approval Criteria

Authorization will be given if one of the following criteria are met and documented:

- a. If an ICD code for herpes zoster is documented on the prescription;

OR

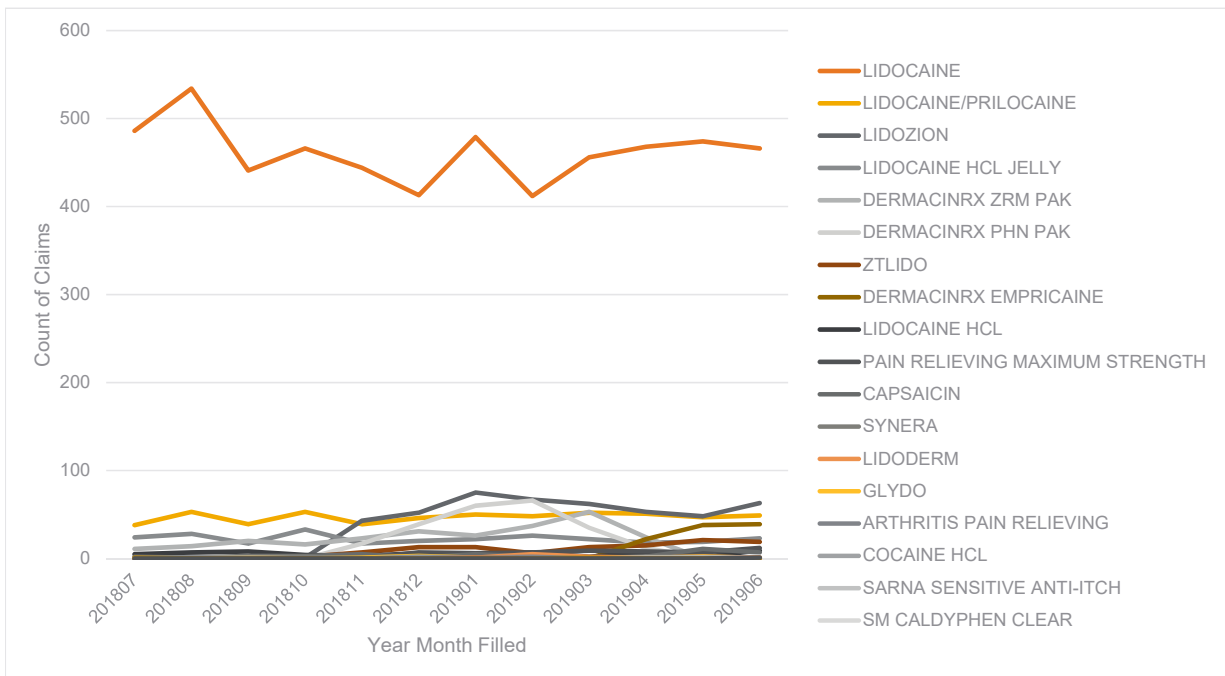
- b. Completion of a prior authorization documenting a diagnosis of Post Herpetic Neuralgia/Neuropathy.

Lidocaine Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
LIDOCAINE PAD 5%	1,765	5,539	139,270	601,983
LIDOCAINE/PRILOCAINE	289	565	10,429	18,284
LIDOZION	177	467	12,624	98,766
LIDOCAINE HCL JELLY	192	269	3,235	7,078
DERMACINRX ZRM PAK	61	255	5,242	798
DERMACINRX PHN PAK	39	229	2,060	417
ZTLIDO	41	109	2,937	6,810
DERMACINRX EMPRICAINE	48	99	3,000	300
LIDOCAINE HCL	49	62	376	2,391
PAIN RELIEVING MAXIMUM STRENGTH	34	56	1,281	2,790
CAPSAICIN	37	42	946	3,000
SYNERA	5	12	117	96
LIDODERM	8	12	99	280
GLYDO	10	11	18	148
ARTHRITIS PAIN RELIEVING	5	8	120	459
COCAINE HCL	4	4	4	16
SARNA SENSITIVE ANTI-ITCH	3	3	70	666
SM CALDYPHEN	2	2	37	354
SM CALDYPHEN CLEAR	1	2	20	354
GNP ALOE VERA/LIDOCAINE	2	2	60	454
SM ALCOHOL PREP PADS/BENZOCAINE	1	1	60	200



O. Lidoderm 5% Patches®

Therapeutic Class: Topical, Local Anesthetics
Last Reviewed by the DUR Board: April 30, 2009

1. Coverage and Limitations

Topical Lidoderm Patches® 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.

Authorization will be given if one of the following criteria are met and documented:

- a. If an ICD code for herpes zoster is documented on the prescription; or
- b. Completion of a prior authorization documenting a diagnosis of Post Herpetic Neuralgia/Neuropathy.

Therapeutic Class Overview

Neuropathic Pain and Fibromyalgia Agents

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2017*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2018[a]*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2018[b]*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), and ZTLido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2017, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2018, Lyrica CR 2017, Neurontin 2018, Nucynta ER 2018, Qutenza 2013, Savella 2017, ZTLido 2018*).
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2018[a]*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2018[a]*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2018[b]*).
 - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in established diabetic neuropathy is uncertain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2018[b]*).
 - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2018[b]*).
 - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (*Feldman et al 2018[b]*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).
 - Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2015*).
- The prevalence of fibromyalgia in the general US population is estimated to be 2 to 3% and increases with age (*Goldenberg 2018[a]*). It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2015*).
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2015*).

PHN

- PHN refers to the persistence of the pain of herpes zoster beyond 4 months from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PHN are older age, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or life (*Bajwa et al 2018*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2018*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2018*). **Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN (*Albrecht 2018*).**
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2018*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✓
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✓
Lyrica (pregabalin)	-
Lyrica CR (pregabalin ER)	-
Neurontin (gabapentin)	✓
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

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

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✓					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✓			
Adjunctive therapy for patients 4 years of age and older with partial onset seizures					✓					
Management of chronic musculoskeletal pain	✓ †									
Management of fibromyalgia	✓				✓					✓
Management of neuropathic pain associated with diabetic peripheral neuropathy	✓				✓	✓		✓ §		
Management of neuropathic pain associated with spinal cord injury					✓					
Management of PHN		✓	✓		✓	✓	✓			
Relief of pain associated with PHN				✓					✓	
Moderate-to-severe primary restless legs syndrome			✓ †							
Treatment of generalized anxiety disorder	✓									
Treatment of major depressive disorder	✓									
Management of moderate to severe chronic pain in adults								✓ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.

‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.

§ Indicated when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Medication is not for use as: an as-needed analgesic; for pain that is mild or not expected to persist for an extended period of time; for acute pain; or for postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

(Prescribing information: Cymbalta 2017, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2018, Lyrica CR 2017, Neurontin 2018, Nucynta ER 2018, Qutenza 2013, Savella 2017, ZTlido 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

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and patient global impression of change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberget al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberget al 2014*). Another head-to-head trial found high-dose duloxetine or pregabalin monotherapy had no significant differences, as measured by Brief Pain Inventory Modified Short Form (BPI-MSF) average pain in comparison, with combination duloxetine and pregabalin therapy (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Derry et al 2019, Quilici et al 2009, Wernicke et al 2007[a], Wiffen et al 2017*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score compared to placebo (*Lyrice prescribing information 2018, Siddall et al 2006, Vranken et al 2008*).

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
 - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with

the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).

- In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve $\geq 30\%$ reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
- Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the differences with regard to the occurrence of the key symptoms of fibromyalgia syndrome and to AEs specific to individual drug (*Hauser et al 2010*).
- A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
- A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving $> 30\%$ improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee and Song 2016*).
- A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adherence scores of 0 ($\geq 90\%$ adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adherence scores of 1 ($\geq 75\%$ to $< 90\%$ adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater ($< 75\%$ adhered) (*ZTlido prescribing information 2018*).
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).
- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, Short form-McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and

morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).

- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported $\geq 50\%$ reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (N = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with $\geq 50\%$ reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN supports the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2017*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial (*Huffman et al 2017*).

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016, recommend the following:
 - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
 - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
 - The opioids, dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
 - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2019 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2019*).

- Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
- Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker.
- Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options.
- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- The AAN recently retired their 2004 practice parameter on the treatment of PHN (*Dubinsky et al 2004*).
- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear (*Attal et al 2010*).

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. **Methemoglobinemia has been reported in association with local anesthetic use.**
- The following key contraindications are included in the prescribing information:
 - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors is contraindicated with duloxetine, milnacipran, and tapentadol ER.
 - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthma, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- The following monitoring parameters are recommended with treatment:

Data as of March 19, 2019 CME/KAL

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- Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin treatment.
- Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, monoamine oxidase inhibitors [MAOIs], linezolid, and methylene blue).
- Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
- Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
- Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
- Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Administer with evening meal Reduce dose in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	Administer with food Reduce dose in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Apply for up to 12 hours within a 24-hour period Caution in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min Administer after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Reduce dose in CrCl < 60 mL/min
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance Do not use in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment Reduce dose in moderate hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Qutenza (capsaicin)	Patch	Transdermal	60-minute application of up to 4 patches every 3 months	Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	Reduce dose in CrCl < 30 mL/min Caution in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; ESRD = end-stage renal impairment
See the current prescribing information for full details

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrate that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2018[b], Schwartz et al 2011*).
 - Of the neuropathic pain and fibromyalgia agents included in the review, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2018*).
 - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2018[b]*).
 - Of the neuropathic pain and fibromyalgia agents included in this review, duloxetine and pregabalin are approved for fibromyalgia.

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Inhaled Anticholinergic Agents





Prior Authorization Guideline

Guideline Name: Inhaled Anticholinergic Agents

1. Criteria

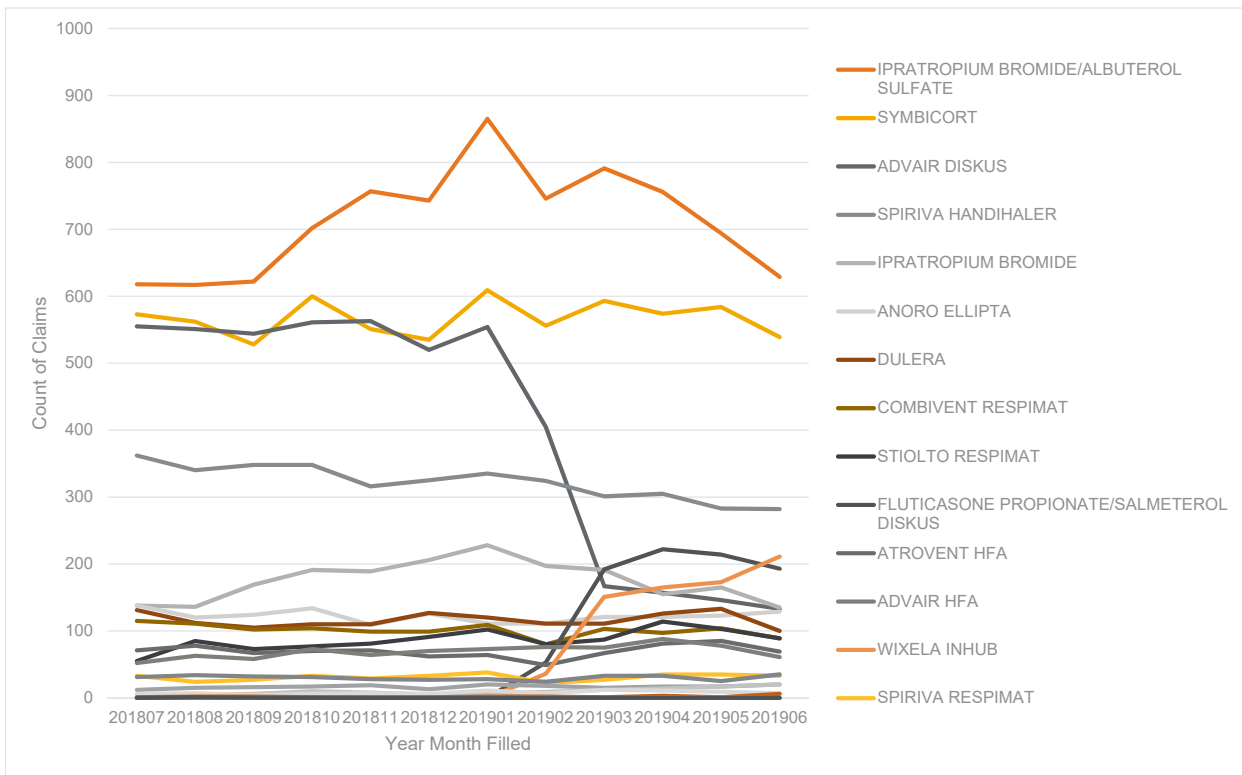
Guideline Type	Prior Authorization
<p data-bbox="198 814 435 846">Approval Criteria</p> <p data-bbox="198 884 407 915">General Criteria</p> <ol data-bbox="248 957 1203 989" style="list-style-type: none"><li data-bbox="248 957 1203 989">1. Only one inhaled anticholinergic agent may be used in a 30-day period.	

Inhaled Anticholinergics Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
ADVAIR DISKUS	1,332	4,856	165,692	327,727
ADVAIR HFA	208	831	26,948	10,368
ANORO ELLIPTA	379	1,467	52,757	107,381
ATROVENT HFA	211	834	26,658	12,345
BEVESPI AEROSPHERE	58	199	6,967	2,572
BREO ELLIPTA	127	361	11,765	22,728
COMBIVENT RESPIMAT	295	1,212	40,760	5,580
DULERA	340	1,396	47,105	20,054
FLUTICASONE PROPIONATE/SALMETEROL	1	1	30	1
FLUTICASONE PROPIONATE/SALMETEROL DISKUS	452	874	32,640	65,100
INCRUSE ELLIPTA	23	93	2,880	2,880
IPRATROPIUM BROMIDE	1,278	2,100	18,406	162,878
IPRATROPIUM BROMIDE/ALBUTEROL SULFATE	3,770	8,540	86,498	960,342
LONHALA MAGNAIR STARTER KIT	1	3	90	180
SPIRIVA HANDIHALER	893	3,869	134,345	135,140
SPIRIVA RESPIMAT	96	369	12,718	1,684
STIOLTO RESPIMAT	255	1,037	37,429	4,952
SYMBICORT	1,668	6,804	229,569	76,802
TRELEGY ELLIPTA	36	114	3,494	6,961
TUDORZA PRESSAIR	11	23	720	23
WIXELA INHUB	368	736	26,435	52,560



DIVISION OF HEALTH CARE FINANCING AND POLICY

MEDICAID SERVICES MANUAL

W. Inhaled Anticholinergic Agents

Therapeutic Class:

Last Reviewed by the DUR Board:

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

1. General Criteria

- a. Only one inhaled anticholinergic agent may be used in a 30-day period.

INTRODUCTION

- The respiratory anticholinergics class includes short- and long-acting agents. Short-acting agents include Atrovent HFA (ipratropium bromide) inhalation aerosol, and ipratropium bromide solution for nebulization (available generically). Long-acting agents, also called long-acting muscarinic antagonists (LAMAs), include Spiriva Handihaler (tiotropium bromide) inhalation powder, Spiriva Respimat (tiotropium bromide) inhalation spray, Incruse Ellipta (umeclidinium) inhalation powder, and Yupelri (revefenacin) solution for nebulizer, which are all administered once daily; Lonhala Magnair (glycopyrrolate) solution for nebulization is administered twice daily. Other relatively long-acting agents are Tudorza Pressair (aclidinium bromide) inhalation powder and Seebri Neohaler (glycopyrrolate) inhalation powder, which are administered twice daily. The predominant use of respiratory anticholinergics is for the treatment of chronic obstructive pulmonary disease (COPD); Spiriva Respimat is also indicated for selected patients with asthma.
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*).
- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (*Centers for Disease Control and Prevention 2018*). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2019*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2019*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2019*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2019*).
- Pharmacologic options for COPD treatment comprise several classes, including beta-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2019*).
- In 2015, tiotropium inhalation spray became the first LAMA to be Food and Drug Administration (FDA)-approved for the treatment of asthma (See Table 2). Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The most effective, commonly recommended long-term control medications for the treatment of asthma are ICSs. Alternative long-term control monotherapy medications, such as leukotriene modifiers, mast-cell stabilizers, and methylxanthines, are considered less effective as monotherapy compared to ICSs. Long-acting beta₂-agonists (LABAs) should not be used as monotherapy for asthma due to increased risk for serious adverse events including death; however, they are considered the most effective adjunctive therapy in patients not adequately controlled with an ICS

alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. **Other add-on controller medications for patients with severe asthma** include the interleukin-5 (IL-5) antagonists **Cinqair** (reslizumab), **Fasenra** (benralizumab), and **Nucala** (mepolizumab); the interleukin-4 (IL-4) receptor antagonist, **Dupilumab** [dupilumab]; and the immunoglobulin E (IgE) antagonist, **Xolair** (omalizumab). The IL-5 antagonists are used for severe eosinophilic asthma, while omalizumab is used in patients with moderate-to-severe allergic asthma.

Dupilumab an add-on option for patients with severe eosinophilic asthma or type 2 asthma uncontrolled on high dose ICS-LABA. Short-acting beta₂-agonists (SABAs) are the medication of choice for the relief of bronchospasm during acute asthma exacerbations (*Global Initiative for Asthma [GINA] 2018, GINA 2019a, GINA 2019b, NHLBI, 2007*).

- This review includes single-agent LAMAs. While some respiratory anticholinergics are available in combination with other bronchodilators such as SABAs and LABAs, combination agents are not included within this review.
- Medispan class: Bronchodilators – Respiratory Anticholinergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Atrovent HFA (ipratropium bromide)	-
Incruse Ellipta (umeclidinium bromide)	-
ipratropium bromide solution	✓
Lonhala Magnair (glycopyrrolate)	-
Seebri Neohaler (glycopyrrolate)	-
Spiriva Handihaler (tiotropium bromide)	-
Spiriva Respimat (tiotropium bromide)	-
Tudorza Pressair (acclidinium bromide)	-
Yupelri (revefenacin)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Atrovent HFA (ipratropium bromide)	Incruse Ellipta (umeclidinium)	ipratropium bromide solution	Lonhala Magnair (glycopyrrolate)	Seebri Neohaler (glycopyrrolate)	Spiriva Handihaler (tiotropium)	Spiriva Respimat (tiotropium)	Tudorza Pressair (acclidinium)	Yupelri (revefenacin)
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	✓		✓						
Maintenance treatment of COPD								✓	
Long-term maintenance treatment of airflow obstruction/bronchospasm in patients with COPD		✓ *		✓	✓	✓ *	✓ *		✓ *
Reducing COPD exacerbations						✓	✓		
Long-term, once-daily maintenance treatment of asthma in patients ≥ 6 years of age							✓		

*Once-daily maintenance treatment

(*Prescribing information: Atrovent HFA 2012, Incruse Ellipta 2017, ipratropium solution 2017, Lonhala Magnair 2018, Seebri Neohaler 2018, Spiriva Handihaler 2018, Spiriva Respimat 2019, Tudorza Pressair 2019, Yupelri 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

COPD

- Efficacy of the LAMAs for the management of COPD is well established through placebo-controlled trials and a number of systematic reviews and meta-analyses. The primary endpoint in most trials has focused on lung function, including measures of the forced expiratory volume in 1 second (FEV₁). Several studies have also evaluated the impact of LAMAs on measures of quality of life and health status, and frequency of COPD exacerbations.
 - All of the LAMAs have demonstrated improved FEV₁ compared to placebo (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016, Aziz et al 2018*).
 - All of the LAMAs have demonstrated improvement in health status and/or COPD symptoms (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016, Aziz et al, 2018, Han et al 2018, Sliwka et al 2018*).
 - Tiotropium and umeclidinium have demonstrated a significant reduction in moderate COPD exacerbations (*Karner et al 2014, Ni et al 2017, Pleasants et al 2016, Sliwka et al 2018*).

Placebo-controlled trials

- Tiotropium administered via the Handihaler device has been compared to placebo in several randomized controlled trials.
 - A randomized double-blind trial (N = 623) demonstrated that tiotropium 18 mcg daily significantly improved trough forced expiratory volume in 1 second (FEV₁) over placebo. Improvements were also demonstrated in peak expiratory flow (PEF) rate, transitional dyspnea index (TDI) focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores compared to placebo (*Donohue et al 2002*).
 - Another randomized double-blind trial (N = 1207) demonstrated that tiotropium 18 mcg daily compared to placebo led to a delayed time to first COPD exacerbation, fewer hospital admissions, fewer days in which patients could not perform their usual daily activities, improved TDI focal scores, and improved results on the SGRQ (*Brusasco et al 2003*).
 - A randomized double-blind trial (N = 457) in maintenance treatment-naïve patients with COPD GOLD stage II demonstrated that tiotropium 18 mcg daily compared to placebo significantly improved FEV₁ and physician's global assessments of overall health status (*Troosters et al 2014*).
 - In a small randomized double-blind trial (N = 105), patients receiving tiotropium 18 mcg daily showed a longer exercise endurance time compared to patients receiving placebo (*Casaburi et al 2005*).
 - A large, randomized, double-blind, 4-year trial (N = 5993) (UPLIFT) demonstrated that tiotropium 18 mcg daily was associated with a significant delay in the time to first exacerbation and time to first hospitalization for an exacerbation. Although the improvement in FEV₁ with tiotropium was maintained throughout the trial, tiotropium did not lead to a significant difference in the rate of decline in FEV₁ over time. Improvements in SGRQ were demonstrated, but were less than what is generally accepted as clinically significant. Mortality was 14.9% in the tiotropium group and 16.5% in the placebo group (*Tashkin et al 2008*). A predefined subgroup analysis of UPLIFT demonstrated that for patients with moderate COPD (GOLD Stage II), the rate of decline for post-bronchodilator FEV₁ was lower in the tiotropium group compared to the placebo group. However, the rate of decline of pre-bronchodilator FEV₁ did not differ between groups (*Decramer et al 2009*).
 - A multicenter, randomized, double-blind trial in patients (N = 841) with mild or moderate COPD (ie, GOLD stage 1 or 2) demonstrated that tiotropium 18 mcg daily significantly improved change in FEV₁ before bronchodilator use from baseline to 24 months compared to placebo (between-group difference, 157 mL; 95% confidence interval [CI], 123 to 192; p < 0.001) (*Zhou et al 2017*). Annual decline in FEV₁ after bronchodilator use was lower with tiotropium vs placebo (difference, 22 mL per year; 95% CI, 6 to 37; p = 0.006) but the annual decline in FEV₁ before bronchodilator use was not significantly different between groups.
- Tiotropium administered via the Respimat inhaler has also been compared to placebo in several randomized controlled trials.
 - Two one-year studies (total N = 1990) evaluated tiotropium 5 mcg or 10 mcg compared to placebo. Combined results for the 5 mcg dose demonstrated the following:
 - improved response on FEV₁ (difference, 127 mL; p < 0.0001)
 - improved response on SGRQ (difference, -3.5 units; p < 0.0001)

- improved response on TDI focal score (difference, 1.05 units; $p < 0.0001$)
- reduced exacerbations (odds ratio [OR], 0.75; $p < 0.01$) (*Bateman et al 2010a*)
- A one-year study (N = 3991) compared tiotropium 5 mcg to placebo and demonstrated the following:
 - improved response on FEV₁ (difference, 102 mL; $p < 0.0001$)
 - a delayed time to first exacerbation (hazard ratio [HR], 0.69; $p < 0.0001$) (*Bateman et al 2010b*)
- A systematic review summarized the data on exacerbation risk reduction with tiotropium compared to placebo (as well as compared to other COPD maintenance treatments). A total of 29 articles were included, of which 20 compared tiotropium to placebo (16 with the Handihaler and 4 with the Respimat device). Although a formal meta-analysis was not conducted as part of this review, overall, the data demonstrated that tiotropium was associated with a longer time to first exacerbation and fewer exacerbations, including severe exacerbations, compared to placebo. Exacerbations were generally comparable with the Handihaler and Respimat formulations (*Halpin et al 2016*).
- A systematic review and meta-analysis of 22 trials and 23,309 participants evaluated the efficacy of tiotropium (delivered via the Respimat or Handihaler device) vs placebo. The analysis showed that tiotropium led to statistically and clinically significant improvements in quality of life vs placebo, as measured by SGRQ. Compared to placebo, tiotropium significantly reduced the number of exacerbations and led to fewer hospitalizations due to exacerbations, but no significant difference was found for all-cause hospitalization or mortality. Pooled analysis showed an improvement in trough FEV₁ with tiotropium vs placebo (mean difference, 119 mL; 95% CI, 113 to 125) (*Karner et al 2014*).
- Acclidinium has also been evaluated in a number of placebo-controlled trials.
 - In a large, randomized double-blind study (N = 828), patients were randomized to receive acclidinium 200 or 400 mcg twice daily or placebo over 24 weeks. The mean change from baseline in trough FEV₁, the primary endpoint, was significantly larger in patients treated with acclidinium 200 or 400 mcg compared to patients treated with placebo. In addition, a significantly higher proportion of patients treated with acclidinium 200 or 400 mcg experienced a clinically significant improvement in SGRQ score and TDI score when compared to patients treated with placebo (*Jones et al 2012*).
 - In the 12-week double-blind ACCORD COPD I study (N = 561), patients randomized to receive acclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV₁ compared to patients in the placebo group. Statistically significant improvements on SGRQ were demonstrated for both dose groups, but on average were less than those considered clinically meaningful. A higher proportion of patients receiving acclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Kerwin et al 2012*).
 - In the 12-week double-blind ACCORD COPD II study (N = 544), patients randomized to receive acclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV₁ compared to patients in the placebo group. SGRQ scores improved in all groups, but differences between acclidinium and placebo were not significant. A higher proportion of patients receiving acclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Rennard et al 2013*).
 - The long-term effects of acclidinium on major adverse cardiovascular events (MACE) and COPD exacerbations in patients with moderate-to-very severe COPD was evaluated in the 36-month, placebo-controlled ASCENT trial (*Wise et al 2018*). Patients receiving acclidinium had a MACE incidence rate of 2.4 per 100 patient-years, compared to 2.8 per 100 patient-years with placebo (HR, 0.89; 95% CI, 0.64 to 1.23; meeting non-inferiority [prespecified margin, 1.8]) (*Tudorza Pressair 2019*). The rate of moderate-to-severe COPD exacerbations during the first year of treatment was also evaluated. Acclidinium significantly reduced the rate of exacerbations compared to placebo (relative risk [RR], 0.83; 95% CI, 0.73 to 0.94).
- A systematic review and meta-analysis of 12 multicenter randomized trials (total N = 9547) evaluated acclidinium vs placebo in patients with stable COPD. The analysis found that acclidinium resulted in a significant improvement in pre-dose FEV₁ compared to placebo (MD, 90 mL; 95% CI, 80 to 100 mL), a reduction in the number of patients with exacerbations requiring hospitalization (OR, 0.64; 95% CI, 0.46 to 0.88), and a reduced SGRQ score (MD, -2.34; 95% CI, -3.18 to -1.51). However, no difference was demonstrated in all-cause mortality or in the number of patients with exacerbations requiring oral steroids and/or antibiotics (*Ni et al 2014*). A similar meta-analysis included 7 trials (total N = 7001) evaluating acclidinium vs placebo for a duration of ≥ 12 weeks. This analysis found that compared to placebo, acclidinium did not significantly reduce the incidence of exacerbations (OR, 0.90; 95% CI, 0.75 to 1.07; $P = 0.22$) or all-cause mortality (OR, 0.92; 95% CI, 0.43 to 1.94; $P = 0.82$). However, a significant difference was demonstrated for the rate of hospitalization due to exacerbation (OR, 0.64; 95% CI, 0.47 to 0.89; $P = 0.008$) and improvement in SGRQ (MD,

- 2.34; 95% CI, -3.18 to -1.51). Secondary endpoints, including FEV₁, forced vital capacity (FVC), and TDI, supported the efficacy of aclidinium on lung function and dyspnea symptoms (*Zou et al 2016*).
- Umeclidinium has been evaluated for the treatment of COPD in several Phase 3, multicenter, randomized, placebo-controlled trials.
 - One trial (N = 206) compared 2 doses of umeclidinium, 62.5 mcg and 125 mcg daily, to placebo over a period of 12 weeks. Patients receiving an ICS at baseline continued treatment at a stable dose. No other long-acting bronchodilators were permitted. Improvements in the primary endpoint, the least squares mean (LSM) change from baseline in FEV₁, were observed for umeclidinium 62.5 mcg daily vs placebo (127 mL; 95% CI, 52 to 202; p < 0.001) and for umeclidinium 125 mcg daily vs placebo (152 mL; 95% CI, 76 to 229; p < 0.001). Improvements were also noted for dyspnea, rescue medication use (62.5 mcg strength only), and SGRQ (*Trivedi et al 2014*).
 - A second trial (N = 1,536) compared umeclidinium 62.5 mcg daily, vilanterol 25 mcg daily, umeclidinium/vilanterol 62.5 mcg/25 mcg daily, and placebo over a period of 24 weeks. Concomitant use of ICSs at a stable dose was permitted. Improvements in the primary endpoint, the LSM change from baseline in FEV₁, were observed for all active treatments. For umeclidinium 62.5 mcg daily, the improvement vs placebo was 115 mL (95% CI, 76 to 155). Improvements were also noted for dyspnea and time to first COPD exacerbation (*Donohue et al 2013*).
 - Two additional randomized, double-blind trials (published together, N = 862 and N = 872) evaluated the addition of umeclidinium to fluticasone propionate/salmeterol in patients with COPD. Patients received once-daily umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo added to twice-daily fluticasone propionate/salmeterol 250/50 mcg for 12 weeks. In both studies, improvement in the primary endpoint, the trough FEV₁ on day 85, was significantly better in both umeclidinium groups vs placebo, with differences of 147 mL (95% CI, 107 to 187) and 127 mL (95% CI, 89 to 164) for the 62.5 mcg strength and 138 (95% CI, 97 to 178) and 148 (95% CI, 111 to 185) for the 125 mcg strength. Significant improvements were also demonstrated for the weighted mean FEV₁ over 0 to 6 hours post-dose and rescue albuterol use, while results on SGRQ and the COPD Assessment Test were mixed (*Siler et al 2016*).
 - A review and meta-analysis evaluated the use of umeclidinium compared to placebo (as well as compared to active controls). The meta-analysis included randomized trials with a duration of ≥ 12 weeks. A total of 10 trials were included. Key results from this meta-analysis were as follows (*Pleasant et al 2016*):
 - The weighted mean difference in FEV₁ change from baseline (primary endpoint) for umeclidinium 62.5 mcg vs placebo was 120 mL (95% CI, 100 to 130) (based on data from 7 studies).
 - The weighted mean difference in TDI change from baseline for umeclidinium 62.5 mcg vs placebo was 0.61 (95% CI, -0.17 to 1.39) (based on data from 2 studies).
 - The weighted mean difference in SGRQ change from baseline for umeclidinium 62.5 mcg vs placebo was -2.34 (95% CI, -4.59 to 0.08) (based on data from 5 studies).
 - Umeclidinium 62.5 mcg significantly improved the time to first COPD exacerbation, with an HR of 0.61 (95% CI, 0.41 to 0.90) (based on data from 1 study).
 - A systematic review and meta-analysis of 4 randomized controlled trials with a duration ≥ 12 weeks evaluated umeclidinium compared to placebo in patients with moderate-to-severe COPD (n = 37,98). Key results from this meta-analysis were as follows (*Ni et al 2017*):
 - Odds of moderate exacerbations requiring steroids and/or antibiotics were reduced with umeclidinium vs placebo (OR, 0.61; 95% CI, 0.46 to 0.80), but there was no difference in odds of severe exacerbations requiring hospitalization between groups (based on data from 4 studies).
 - Umeclidinium reduced SGRQ total score compared to placebo (MD, -4.79 units; 95% CI, -8.84 to -0.75) and the odds of having an improvement ≥ 4 units in SGRQ total score was higher with umeclidinium vs placebo (OR, 1.45; 95% CI, 1.16 to 1.82) (based on data from 3 studies).
 - TDI focal score was improved with umeclidinium vs placebo (MD, 0.76 units; 95% CI, 0.43 to 1.09 units) (based on data from 3 studies).
 - Change from baseline in trough FEV₁ was higher with umeclidinium vs placebo (MD, 0.14 L; 95% CI, 0.12 to 0.17 L) (based on data from 4 studies).
 - Glycopyrrolate has been evaluated for the treatment of COPD in Phase 3, randomized, multicenter, double-blind, placebo-controlled trials.
 - Two 12-week trials (N = 441 and 428) evaluated the efficacy of glycopyrrolate inhalation powder 15.6 mcg twice daily vs placebo. Both trials met their primary endpoint, demonstrating differences from placebo in the mean change from baseline in FEV₁ area under the curve (AUC) from 0 to 12 hours (FEV₁ AUC₀₋₁₂) of 139 mL (95% CI, 95 to 184; p < 0.001) and 123 mL (95% CI, 81 to 165; p < 0.001), respectively. Improvement in several secondary endpoints was

also demonstrated, including trough FEV₁, and SGRQ score. The difference in the TDI score was significant in one of the 2 studies (*Clinicaltrials.gov 2015, Kerwin et al 2016, LaForce et al 2016*).

- The efficacy of nebulized glycopyrrolate was evaluated in 2 replicate 12-week randomized controlled trials (GOLDEN 3 and 4; N = 653 and N = 641, respectively) in patients with moderate-to-very severe COPD. Compared with placebo, patients in the intention to treat analysis who were randomized to nebulized glycopyrrolate 25 mcg or 50 mcg twice daily experienced significant increases in the primary endpoint, FEV₁ from baseline (mean placebo-adjusted differences, 0.096 and 0.104, respectively, in GOLDEN 3; 0.081 and 0.074, respectively, in GOLDEN 4; all p < 0.0001). Improvements from baseline were also observed with both doses of nebulized glycopyrrolate vs placebo in FVC and SGRQ scores (*Kerwin et al 2017*).

- **Revefenacin has been evaluated in dose-ranging trials and 2 replicate Phase 3, randomized, multicenter, double-blind, placebo-controlled trials in patients with COPD.**

- Revefenacin was compared to placebo in a randomized-controlled trial of 355 COPD patients; ICSs and SABAs were also allowed for the duration of the trial period. Revefenacin at a dose of 88 mcg, 175 mcg and 350 mcg daily yielded significant improvements in trough FEV₁ at day 28 vs placebo (187.4, 166.6 and 170.6 mL, respectively; p < 0.001 for all comparisons). Doses ≥ 88 mcg also led to the following improvements over placebo: > 80% of patients achieved a ≥ 100 mL increase from baseline FEV₁ at 4 hours post dose; sustained bronchodilation for 24 hours post dose; and reduction in daily albuterol puffs by > 1 puff per day. Lastly, the 350 mcg dose did not demonstrate additional efficacy compared to the 175 mcg dose (*Pudi et al 2018*).

- In the 2 replicate Phase 3 trials that evaluated revefenacin treatment in moderate-to-very severe COPD, 619 patients in Study 0126 and 611 patients with in Study 0127 were randomized to revefenacin 88 mcg, revefenacin 175 mcg, or placebo. The primary endpoint, day 85 mean trough FEV₁, was improved with revefenacin compared to placebo in both trials (placebo-adjusted mean increase in trough FEV₁ was 79.2 mL and 146.3 mL for revefenacin 88 mcg and 175 mcg, respectively, in Study 0126, and 160.5 mL and 147.0 mL for revefenacin 88 mcg and 175 mcg, respectively, in Study 0127; both p < 0.0001). The overall treatment effect on FEV₁ was also significantly improved with revefenacin, both doses, as compared to placebo in both studies (*Ferguson et al 2019*).

Comparisons between different anticholinergics and formulations

- A small number of clinical trials have compared tiotropium to ipratropium.
 - A randomized, double-blind, double-dummy study (N = 288) compared tiotropium 18 mcg daily to ipratropium 40 mcg 4 times daily over 15 weeks. This study demonstrated that the FEV₁ response was significantly greater for tiotropium compared to ipratropium at all time points (p < 0.05). Differences in trough FEV₁ values were most pronounced, whereas differences in peak FEV₁ did not reach statistical significance. Improvements were also greater for tiotropium for morning and evening PEF rate and use of rescue albuterol (*van Noord et al 2000*).
 - A second double-blind, double-dummy study (N = 535) also compared tiotropium 18 mcg daily to ipratropium 40 mcg 4 times daily. At the end of 1 year, trough FEV₁ was significantly better in the tiotropium group (difference, 150 mL; p < 0.001). FVC results paralleled those for FEV₁. Tiotropium also led to improved PEF rates and reduced use of rescue albuterol (*Vincken et al 2002*).
 - Two identical double-blind, double-dummy 12-week trials (total N = 719) compared tiotropium Respimat in both 5 mcg and 10 mcg daily doses to placebo and to ipratropium bromide. Results for the 5 mcg dose demonstrated that trough FEV₁ was improved significantly more with tiotropium vs placebo (difference, 118 mL; p < 0.0001) and compared to ipratropium (difference, 64 mL; p < 0.01) (*Voshaar et al 2008*).
- A meta-analysis demonstrated that compared to patients receiving ipratropium, patients receiving tiotropium were more likely to experience improvement in SGRQ scores and TDI scores. Patients receiving tiotropium also experienced a reduced rate of exacerbations compared to patients receiving ipratropium (*Yohannes et al 2011*).
- A systematic review and meta-analysis (N = 2 studies; 1073 patients) evaluated the safety and efficacy of tiotropium compared to ipratropium (*Cheyne et al 2015*). In one study, patients used tiotropium by Handihaler for 12 months, and in the other, patients used tiotropium by Respimat for 12 weeks. Primary endpoints included the trough FEV₁ at 3 months and serious adverse events.
 - Trough FEV₁ at 3 months was significantly increased with tiotropium compared to ipratropium (MD, 109 mL; 95% CI, 81 to 137; I² = 62%).
 - Fewer patients experienced ≥ 1 non-fatal serious adverse events with tiotropium compared to ipratropium (OR, 0.5; 95% CI, 0.34 to 0.73). Patients taking tiotropium were also less likely to experience a COPD-related serious adverse event (OR, 0.59; 95% CI, 0.41 to 0.85).

- Benefits were also demonstrated for tiotropium compared to ipratropium for secondary endpoints including exacerbations, hospital admissions, and quality of life. There was no significant difference in mortality between the 2 treatments.
- The large, randomized, double-blind TIOSPIR trial (N = 17,135) compared tiotropium Respimat at a dose of 2.5 mcg or 5 mcg daily to tiotropium Handihaler (18 mcg daily). During a mean follow-up of 2.3 years, tiotropium via Respimat and Handihaler were shown to have similar safety and efficacy profiles (*Wise et al 2013*).
 - Risk of death for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.96; 95% CI, 0.84 to 1.09.
 - Risk of first exacerbation for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.98; 95% CI, 0.93 to 1.03.
- A systematic review evaluated tiotropium Respimat 5 mcg daily vs tiotropium Handihaler 18 mcg daily on pharmacokinetic, efficacy, and safety data. Data were included from a total of 22 comparative studies (10 published studies, 1 submitted manuscript, and 11 Congress abstracts). Key results from this review were as follows (*Dahl et al 2016*):
 - Several clinical trials demonstrated similar pharmacokinetic profiles between the 2 formulations. Although it had previously been suggested that systemic exposure may be greater with tiotropium Respimat, a recent study showed that exposure may actually be slightly lower with the Respimat formulation.
 - Results of several randomized trials demonstrated that the efficacy and safety profiles are comparable between the 2 formulations, and results from post-hoc and pooled analyses provide further support for similarity on lung function, exacerbations, and safety outcomes in various patient subtypes.
 - Similar results for health-related quality of life were demonstrated with each formulation based on the SGRQ total score.
- A double-blind, double-dummy, randomized Phase 3b trial (N = 414) compared tiotropium 18 mcg daily to acclidinium 400 mcg twice daily. This trial demonstrated no significant differences between active treatments at week 6 in the change from baseline in FEV₁ AUC over 24 hours (AUC₀₋₂₄). FEV₁ AUC₀₋₁₂ was numerically greater with tiotropium vs acclidinium, and AUC₁₂₋₂₄ was numerically greater with acclidinium vs tiotropium; however, differences between active treatments were not statistically significant. The 2 groups also had comparable results for most COPD symptom measures (*Beier et al 2013*).
- A 48-week, open-label trial (GOLDEN 5; N = 1086) compared glycopyrrolate nebulizer solution 50 mcg twice daily to tiotropium 18 mcg daily in 1086 patients with moderate-to-very severe COPD. The trial demonstrated that the rates of treatment-emergent adverse events were generally similar between groups, while rates of respiratory events were somewhat higher with glycopyrrolate vs tiotropium (35.2% vs 28.8%, respectively); the authors attributed this in part to incorrect nebulizer technique early in treatment. There were no significant differences between groups in the change from baseline in FEV₁ or SGRQ. There was a similar and numerically lower incidence of exacerbations with glycopyrrolate nebulizer solution vs tiotropium (18.5% and 22.5%, respectively) (*Ferguson et al 2017*).
- Results were reported in abstract form of an open-label randomized control trial comparing tiotropium 18 mcg daily with acclidinium 400 mcg twice daily in addition to background therapy in adults with moderate-to-severe COPD. After 8 weeks of treatment, the primary endpoint, FEV₁ AUC₀₋₃ was not significantly different between groups. Secondary outcomes evaluating other measures of lung function were not significantly different; however, SGRQ and Modified Medical Research Council scores were significantly improved with acclidinium (*Nakamura et al 2017*).
- A network meta-analysis (N = 21 studies; 22,542 patients) demonstrated no significant differences between tiotropium 18 mcg daily and acclidinium 400 mcg twice daily in FEV₁, SGRQ, or TDI score (*Karabis et al 2013*).
- A 12-week, blinded, double-dummy, randomized trial (N = 1107) compared umeclidinium 62.5 mcg daily delivered via the Ellipta device and tiotropium 18 mcg daily delivered via the Handihaler device (*Feldman et al 2016*). The primary endpoint, LSM change from baseline in trough FEV₁ at day 85 in the per-protocol population (N = 976), was greater with umeclidinium vs tiotropium (difference, 59 mL; 95% CI, 29 to 88; p < 0.001). Similar results were seen in the intention-to-treat population (difference, 53 mL; 95% CI, 25 to 81; p < 0.001). Improvements in the weighted mean FEV₁ over 0 to 24 hours post-dose were similar between treatments, but greater with umeclidinium vs tiotropium over 12 to 24 hours post-dose (difference, 70 mL; 95% CI, 14 to 127; p = 0.015). No differences were observed between umeclidinium and tiotropium in patient-reported outcomes (TDI and SGRQ), and the safety profiles were similar with both treatments. More patients preferred the Ellipta device compared to the Handihaler, including an overall device preference and scores for ease of use.
 - There were several limitations to this trial, including a short duration and incomplete blinding (markings differed among active tiotropium capsules and placebo, and stickers were used to obscure inhaler markings).

- A network meta-analysis (N = 24 studies; 21,311 participants) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily, glycopyrronium 50 mcg daily (not the FDA-approved dosing), and umeclidinium 62.5 mcg daily in patients with COPD. All active treatments demonstrated favorable outcomes vs placebo for 12-week trough FEV₁, 24-week trough FEV₁, 24-week SGRQ, 24-week TDI, and 24-week rescue inhaler use (*Ismaila et al 2015*).
 - Based on 17 studies (11,935 participants) for the primary endpoint, the mean change from baseline in trough FEV₁ vs placebo at 12 weeks ranged from 101.4 to 136.7 mL, and was greatest for umeclidinium, followed by glycopyrronium, tiotropium, and aclidinium. However, the 95% credible interval (CrI) crossed zero in all between-treatment comparisons, so superiority was not demonstrated for any single LAMA over another.
- A network meta-analysis (N = 27 studies; 48,140 participants) compared tiotropium, aclidinium, and glycopyrronium for preventing COPD exacerbations (*Oba et al 2015*). All of the studied LAMAs reduced moderate-to-severe exacerbations compared to placebo; however, there were no significant differences demonstrated among the active treatments.
 - The analysis also evaluated the rate of severe exacerbations. Tiotropium dry powder inhaler was the only LAMA demonstrated to reduce severe exacerbations vs placebo (HR, 0.73; 95% CI, 0.6 to 0.86). However, the 95% CrI crossed zero in all between-treatment comparisons. The authors concluded that there were no statistically significant differences among LABAs in preventing COPD exacerbations.

Comparisons between anticholinergics and beta₂-agonists or ICS/LABA combinations

- In a meta-analysis of 4 trials, there was no statistically significant differences in short-term FEV₁ changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a beta₂-adrenergic agonist (albuterol, metaproterenol, or fenoterol) (*McCrory et al 2002*).
- Tiotropium has been compared to the LABAs salmeterol and indacaterol in several large comparative trials.
 - Two placebo-controlled trials of tiotropium 18 mcg daily also included an active control arm in which patients received salmeterol 50 mcg twice daily. In the first trial (N = 623), the improvement in trough FEV₁ at 24 weeks was greater with tiotropium compared to salmeterol (difference, 52 mL; p < 0.01). Differences also favored tiotropium for FVC (difference, 112 mL; p < 0.01) and PEF rate (difference, 5.9 L/minute; p < 0.01). Tiotropium was also better than salmeterol in improving TDI focal score (difference, 0.78 units; p < 0.05). The difference between active treatments in SGRQ was not statistically significant (*Donohue et al 2002*). In the second trial (N = 1207), improvements in FEV₁, FEV₁ area under the curve over 3 hours (AUC₀₋₃), and FVC were greater for tiotropium vs salmeterol; however, there were no significant differences among active treatment groups for time to first COPD exacerbation, hospital admissions, or TDI focal scores (*Brusasco et al 2003*).
 - A large double-blind randomized trial (N = 7348) (POET-COPD) demonstrated that tiotropium 18 mcg daily increased the time to first COPD exacerbation, the risk of moderate exacerbations, and the risk of severe exacerbations compared to treatment with salmeterol (*Vogelmeier et al 2011*). Prolongation of time to the first exacerbation was also demonstrated in prespecified subgroups of patients with GOLD stage II COPD and patients who were maintenance-therapy-naïve (*Vogelmeier et al 2013*).
 - A randomized trial (N = 1683) compared 2 doses of the once-daily LABA indacaterol (150 mcg and 300 mcg) to tiotropium 18 mcg daily and to placebo. In this trial, patients receiving placebo or indacaterol were blinded, but tiotropium was open-label because blinded tiotropium was not available. The primary endpoint, trough FEV₁ at 12 weeks, was greater for indacaterol (both doses) than for tiotropium (difference, 40 mL; p ≤ 0.01). Greater improvements were also demonstrated for indacaterol vs tiotropium for the proportions of patients achieving a clinically important improvement in TDI total score (p ≤ 0.01), use of rescue albuterol (p ≤ 0.001), and change from baseline in morning and evening PEF (p < 0.05). Rates of exacerbations did not differ among active treatment groups (*Donohue et al 2010*).
 - A randomized, double-blind, double-dummy trial compared tiotropium 18 mcg daily to indacaterol 150 mcg daily. In this trial, trough FEV₁ with tiotropium was determined to be non-inferior to indacaterol, but not superior (treatment difference, 0 mL; 95% CI, -20 to 20). However, FEV₁ and FVC were demonstrated to be greater with indacaterol on day 1 when evaluated 5 minutes, 30 minutes, and 1 hour after dosing. More patients receiving indacaterol compared to those taking tiotropium experienced a clinically significant improvement in TDI scores (OR, 1.49; p < 0.001) and SGRQ scores (OR, 1.43; p < 0.001). In addition, use of rescue medication was lower in the indacaterol group (*Buhl et al 2011*).
- Tiotropium has also been compared to combination ICS/LABAs.
 - Tiotropium 18 mcg daily has been compared to fluticasone/salmeterol 250 mcg/50 mcg in a randomized, double-blind, double-dummy, 2-year trial (N = 1323). The primary endpoint in this trial, the rate of exacerbations over 2 years,

was comparable in the tiotropium (1.32/year) and fluticasone/salmeterol (1.28/year) groups ($p = 0.656$). Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to fluticasone/salmeterol (HR, 1.29; 95% CI, 1.08 to 1.54; $p = 0.005$). In addition, mortality was significantly lower in the fluticasone/salmeterol group (3%) than in the tiotropium group (6%) (HR, 0.48; 95% CI, 0.27 to 0.85; $p = 0.012$) (Wedzicha *et al* 2008).

- Tiotropium 18 mcg daily has also been compared to fluticasone furoate/vilanterol 100/25 mcg daily in a randomized, double-blind, double-dummy, 12-week trial (N = 623) in patients with COPD and cardiovascular disease (CVD) or CVD risk (≥ 1 risk factor of hypertension, hypercholesterolemia, or treated diabetes). The primary endpoint, change from baseline in weighted mean FEV₁ over 24 hours at 12 weeks, was similar in the 2 treatment arms (LSM change, 95 mL and 117 mL in the tiotropium and fluticasone furoate/vilanterol groups, respectively, with a difference of 22 mL [95% CI, -12 to 55; $p = 0.201$]). Trough FEV₁ after 12 weeks was improved to a similar extent in both groups. Some secondary endpoints seemed to favor tiotropium (change from baseline in FVC and inspiratory capacity), while other endpoints seemed to favor fluticasone furoate/vilanterol (onset of bronchodilation, rescue medication use, dyspnea, SGRQ, and COPD Assessment Test scores). Safety was generally similar, although pneumonia was reported more frequently in the fluticasone furoate/vilanterol group. Cardiovascular monitoring did not demonstrate an increased cardiovascular risk. The cardiovascular safety profile was similar between groups; however, there were 2 deaths from cardiovascular events in the tiotropium group (both patients had hypertension and 1 smoked and had a family history of CVD). Fewer patients experienced a COPD exacerbation in the fluticasone furoate/vilanterol group (2%) than the tiotropium group (4%) (Covelli *et al* 2016).
- In a Cochrane review which included the Covelli *et al* 2016 trial and one additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when considering the following outcomes: mortality, COPD exacerbation, pneumonia, SGRQ score, hospital admissions, or use of rescue medication (Sliwka *et al* 2018).
- Meta-analyses comparing tiotropium to LABAs do not consistently demonstrate superiority on key endpoints for either treatment. One meta-analysis (N = 7 trials; 12,223 participants) demonstrated a reduction in the proportion of patients experiencing ≥ 1 exacerbations with tiotropium compared to a LABA; however, 1 trial contributed the most weight to this analysis (Chong *et al* 2012).
- A systematic review and network meta-analysis (N = 71 trials; 73,062 participants) evaluated the efficacy of various treatment options for patients with COPD that could not be controlled by short-acting therapies alone. This analysis ranked ICS/LABA combinations first for results on SGRQ and trough FEV₁. LAMAs and LABAs were ranked second and third for each measure, and these 2 categories of medications had similar effects overall (Kew *et al* 2014).
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV₁ compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV₁. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV₁ improvement; similar trends were observed for the transition dyspnea index and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (Aziz *et al* 2018).
- A systematic review and network meta-analysis (N = 10 trials; 10,894 participants) compared the effects of LABA/tiotropium combination therapy vs either therapy alone (Farne *et al* 2015).
 - Compared to tiotropium alone, combination treatment resulted in a slightly larger improvement in SGRQ (MD, -1.34; 95% CI, -1.87 to -0.8; 6709 participants; 5 studies). There were no significant differences in hospital admissions (4 studies; 4,856 participants) or all-cause mortality (10 studies; 9633 participants). The improvement in pre-bronchodilator FEV₁ at the end of the study showed a statistically significant increase in the combination group compared to the tiotropium group (MD, 60 mL; 95% CI, 50 to 70; 10 studies; 9573 participants). Results for exacerbations were not pooled due to clinical heterogeneity.
 - Compared to LABA alone, combination treatment resulted in a small but statistically significant improvement in SGRQ (MD, -1.25; 95% CI, -2.14 to -0.37; 3378 participants; 4 studies). There were no significant differences in all-cause hospitalizations, hospitalizations for exacerbations, or all-cause mortality (3 studies; 3514 participants for all endpoints). The improvement in pre-bronchodilator FEV₁ at the end of the study showed a statistically significant increase in the combination group compared to the LABA group (MD, 70 mL; 95% CI, 60 to 90; 4 studies; 3513

participants). There was a significantly lower risk of exacerbation with combination treatment vs LABA monotherapy (OR, 0.8; 95% CI, 0.69 to 0.93; 3 studies; 3514 participants).

- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (RR, 0.93; 99% CI, 0.85 to 1.02; $p = 0.0498$) (*Calverley et al 2018*).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among patients in the included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV₁ peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV₁ trough by 63 ml compared to tiotropium alone (95% CI, 39.2 to 86.8; $p < 0.01$). During the same time period, LABA/LAMA improved the mean SGRQ responder rate by 19% (RR, 1.19; 95% CI, 1.09 to 1.28; $p < 0.01$) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; $p < 0.01$) compared to tiotropium (*Han et al 2018*).
- There is little data on the use of aclidinium compared to beta₂-agonists. A small study (N = 79) compared various doses of aclidinium to the LABA formoterol in a crossover study in which each treatment was given for 7 days. The primary endpoint, difference in FEV₁ AUC₀₋₁₂ on day 7, was not significantly different in the aclidinium 400 mcg twice daily and formoterol 12 mcg twice daily groups (208 mL and 210 mL, respectively). There also was no difference between treatment with aclidinium 400 mcg and formoterol with regard to changes in FEV₁ AUC₀₋₂₄; however, patients treated with aclidinium 400 mcg experienced a statistically significant improvement in FEV₁ AUC₁₂₋₂₄ compared to treatment with formoterol (56 mL; $p < 0.01$) (*Singh et al 2012*).

ASTHMA

- Clinical trials have demonstrated efficacy with the tiotropium Respimat vs placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- Efficacy of tiotropium for the treatment of asthma has also been established through many systematic reviews and meta-analyses.
 - A series of systematic reviews and meta-analyses have reported the efficacy of tiotropium in the treatment of asthma (*Rodrigo et al 2015a, Rodrigo et al 2015, Rodrigo et al 2017*). These analyses demonstrated the ability of tiotropium to improve lung function endpoints, including FEV₁ and/or PEF, while the impact on overall asthma control, asthma-related quality of life, and asthma exacerbations were mixed.
 - Focused meta-analyses have also demonstrated the efficacy of tiotropium for the management of asthma when added to an ICS compared to use of the ICS alone (*Anderson et al 2015, Wang et al 2018*), and when added to an ICS/LABA compared to ICS/LABA alone (*Kew et al 2016*). Studies generally supported the efficacy of tiotropium based on lung function, with less evidence for an impact on exacerbations and asthma-related quality of life.
 - A meta-analysis compared the addition of a LAMA (tiotropium) to addition of a LABA (salmeterol) in patients not adequately controlled on an ICS (*Kew et al 2015*). No significant differences were demonstrated in the rate of exacerbations requiring oral corticosteroids.

Placebo-controlled and trials

- Clinical trials have compared tiotropium Respimat to placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- A 12-week, Phase 3, multicenter, randomized trial (N = 465) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in adults with asthma who were symptomatic despite treatment with a low- to medium-dose ICS (200 to 400 mcg budesonide or equivalent), which was continued during the trial. The primary endpoint, change from baseline in peak FEV₁ within 3 hours of dosing (FEV₁ [0 to 3 hr]), was greater for both tiotropium doses compared to placebo, with adjusted MDs of 159 mL and 128 mL for the 2.5 mcg and 5 mcg doses, respectively ($p < 0.001$ for both comparisons vs placebo). Both doses of tiotropium were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV₁ and FEV₁ AUC_{0 to 3} responses, and the other endpoints of morning and evening PEF. Adverse events were comparable across the treatment groups (*Paggiaro et al 2016*).
- Two 24-week, Phase 3, multicenter, randomized trials (total N = 2103) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, salmeterol 50 mcg twice daily, or placebo in adults with asthma who were symptomatic despite treatment with a medium-dose ICS (400 to 800 mcg budesonide or equivalent) alone or in combination with a beta₂-agonist. During the study, patients continued their ICS, but pre-study LABAs were discontinued. Co-primary endpoints were the

peak FEV₁ (0 to 3 hr), trough FEV₁, and responder rate according to the 7-question Asthma Control Questionnaire (ACQ-7). Pooled data demonstrated the following (*Kerstjens et al 2015*):

- The differences vs placebo in peak FEV₁ were 223 mL (95% CI, 185 to 262) in the tiotropium 2.5 mcg group, 185 mL (95% CI, 146 to 223) in the tiotropium 5 mcg group, and 196 mL (95% CI, 158 to 234) in the salmeterol group (all p < 0.0001 vs placebo).
- The differences in trough FEV₁ were 180 mL (95% CI, 138 to 221) in the tiotropium 2.5 mcg group, 146 mL (95% CI, 105 to 188) in the tiotropium 5 mcg group, and 114 mL (95% CI, 73 to 155) in the salmeterol group (all p < 0.0001 vs placebo).
- There were more ACQ-7 responders (improvement of ≥ 0.5) in the tiotropium 2.5 mcg group (OR, 1.33; 95% CI, 1.03 to 1.72; p = 0.031), tiotropium 5 mcg group (OR, 1.32; 95% CI, 1.02 to 1.71; p = 0.035), and salmeterol group (OR, 1.46; 95% CI, 1.13 to 1.89; p = 0.0039), than in the placebo group.
- Severe asthma exacerbations were recorded in 4%, 6%, 6%, and 8% of patients in the tiotropium 2.5 mcg, 5 mcg, salmeterol, and placebo groups, respectively. At least 1 episode of asthma worsening was recorded in 22%, 28%, 25%, and 32% of patients, respectively. The investigators noted a statistically significant reduction in risk of first severe exacerbation with tiotropium 2.5 mcg (p = 0.0084) and of first asthma worsening with tiotropium 2.5 mcg and salmeterol (p = 0.0007 and 0.013, respectively) vs placebo.
- The numbers of adverse events and serious adverse events were comparable among groups.
- Additional support for the safety and efficacy of tiotropium for asthma treatment was provided by the results of two 48-week, Phase 3, multicenter, randomized trials (total N = 912) comparing tiotropium Respimat 5 mcg daily to placebo in adults with asthma not adequately controlled on an ICS (≥ 800 mcg budesonide or equivalent) and a LABA. Tiotropium was superior to placebo for endpoints including mean change in peak FEV₁, trough FEV₁, and the time to first severe exacerbation. Adverse events were similar in the 2 groups. However, it should be noted that this study only evaluated a dose that is higher than the FDA-approved dose for asthma (*Kerstjens et al 2012*).
- Two randomized Phase 3 trials evaluated the use of tiotropium Respimat in adolescents 12 to 17 years of age.
 - A 12-week trial (N = 392) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with severe asthma who were on background treatment of an ICS plus ≥ 1 controller medications, such as a LABA. The difference vs placebo for the primary endpoint, peak FEV₁ (0 to 3 hr), was 111 mL (95% CI, 2 to 220) for the 2.5 mcg dose and 90 mL (95% CI, -19 to 198) for the 5 mcg dose (*Hamelmann et al 2017*).
 - A 48 week trial (N = 398) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with moderate asthma who were on background treatment of at least an ICS. The difference vs placebo in the primary endpoint, peak FEV₁ (0 to 3 hr) was 134 mL (95% CI, 34 to 234) for the 2.5 mcg dose and 174 mL (95% CI, 76 to 272) for the 5 mcg dose (*Clinicaltrials.gov 2014, Spiriva Respimat prescribing information 2018*).
- According to the prescribing information, efficacy of tiotropium in pediatric patients 6 to 11 years of age was based on extrapolation of efficacy in adults, and on 2 randomized, double-blind, placebo-controlled trials of 12 and 48 weeks duration. A total of 801 patients 6 to 11 years of age were enrolled in the 2 trials (271 receiving tiotropium 2.5 mcg daily, 265 receiving tiotropium 5 mcg daily, and 265 receiving placebo). The primary endpoint in both trials was the change from baseline in the peak FEV₁ (0 to 3 hr), with the evaluation defined at week 12 in the 12-week trial and at week 24 in the 48-week trial (*Spiriva Respimat prescribing information 2018*).
 - The 12-week trial enrolled patients with severe asthma who were on background treatment of ICS plus ≥ 1 controller medication (eg, LABA). The mean difference vs placebo in the primary endpoint was 40 mL (95% CI, -30 mL to 100 mL; not significant).
 - The 48-week trial enrolled patients with moderate asthma on background treatment of at least an ICS. The mean difference vs placebo in the primary endpoint was 170 mL (95% CI, 110 to 230).
- An additional trial in children 6 to 11 years of age with severe symptomatic asthma randomized patients to double-blind tiotropium 5 mcg, 2.5 mcg, or placebo administered via a Respimat device in addition to background therapy with medium-dose ICS. After 12 weeks, tiotropium 5 mcg, but not 2.5 mcg, improved the primary end point, peak FEV₁ within 3 hours after dosing compared with placebo (MD, 139 mL; 95% CI, 75 to 203 and 35 mL; 95% CI, -28 to 99 for 5 and 2.5 mcg doses, respectively). Results were similar for the key secondary endpoint, trough FEV₁ (*Szeffler et al 2017*).

Systematic reviews and network meta-analyses

- A systematic review and meta-analysis (N = 13 studies; 4966 patients) evaluated the efficacy and safety of tiotropium in patients with asthma. Tiotropium was given via the Respimat device in most studies, and the duration of the included studies ranged from 4 to 52 weeks (*Rodrigo et al 2015a*).
 - In 10 studies evaluating the addition of tiotropium to an ICS vs ICS alone in patients with mild or moderate asthma, the analysis demonstrated significant improvements in morning and evening PEF (MD, 22 to 24 L/min; $p < 0.00001$) and peak and trough FEV₁ (MD, 150 mL; 95% CI, 110 to 180 and 140 mL; 95% CI, 110 to 160, respectively) with the addition of tiotropium. Tiotropium also significantly improved ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ) scores from baseline (MD, -0.14 units; 95% CI, -0.19 to -0.09 and 0.07 units; 95% CI, 0.01 to 0.13, respectively). Tiotropium was also associated with a decrease in the number of patients with ≥ 1 asthma exacerbation (10.5% vs 13.3%; RR, 0.74; 95% CI, 0.57 to 0.95).
 - In 4 studies comparing the addition of either tiotropium or LABA to an ICS in patients with moderate asthma, tiotropium improved morning PEF more than LABA, but the magnitude of the difference was small (6.6 L/min). There were no significant differences in evening PEF or peak or trough FEV₁. The addition of tiotropium was inferior to the addition of LABA for AQLQ (MD, -0.12 units; 95% CI, -0.06 to -0.18). There were no significant differences in ACQ-7 total score or the number of patients with ≥ 1 exacerbation.
 - In 3 studies comparing triple therapy (tiotropium with ICS/LABA) vs LABA with a high-dose ICS in patients with severe asthma, the analysis demonstrated significant improvements with triple therapy in morning and evening PEF (MD, 16 L/min; $p < 0.0004$ and 20 L/min; $p < 0.00001$, respectively). Peak and trough FEV₁ was also significantly greater with triple therapy (MD, 120 mL; 95% CI, 90 to 160 and 80 mL; 95% CI, 40 to 110, respectively). Triple therapy was associated with significant improvements in ACQ-7 and AQLQ (MD, -0.2 units; 95% CI, -0.25 to -0.09 and 0.12 units; 95% CI, 0.05 to 0.18, respectively). Patients treated with triple therapy also had a lower likelihood of experiencing ≥ 1 exacerbation (18.2% vs 24%; RR, 0.7; 95% CI, 0.53 to 0.94).
- A systematic review and meta-analysis (N = 3 studies; 895 patients) evaluated the use of tiotropium Respimat in adolescents 12 to 18 years of age with moderate-to-severe asthma. Patients were also receiving an ICS or ICS/LABA and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV₁ (*Rodrigo et al 2015b*).
 - Tiotropium was associated with significant improvements in peak and trough FEV₁ with mean changes from baseline of 120 mL and 100 mL vs placebo, respectively ($p < 0.001$ for both comparisons).
 - Benefits were also shown with tiotropium for the secondary endpoint of exacerbation risk. There were no significant differences in the rate of ACQ-7 response, rescue medication use, withdrawals, adverse events, or serious adverse events.
- A systematic review and meta-analysis (N = 3 studies; approximately 900 patients) evaluated the use of tiotropium Respimat in children 6 to 11 years of age with moderate-to-severe symptomatic asthma. Patients were also receiving maintenance therapy with ICS or ICS plus ≥ 1 controller medication and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV₁ (*Rodrigo et al 2017*).
 - Tiotropium demonstrated significant improvements in peak FEV₁ of 102 mL and trough FEV₁ of 82 mL vs placebo ($p < 0.0001$ for both comparisons).
 - Tiotropium significantly increased the rate of ACQ-7 responders ($p = 0.04$) and decreased the number of patients ≥ 1 exacerbations ($p = 0.002$) vs placebo.
 - There were no significant differences in rescue medication use, study withdrawals, adverse events, or withdrawals due to adverse events.
- A systematic review and meta-analysis (N = 5 studies; 2563 patients) evaluated the safety and efficacy of an ICS plus LAMA vs ICS alone in patients with asthma. The LAMA used was tiotropium Respimat in all studies, and the duration of treatment ranged from 12 to 52 weeks. All studies used a double-blind, double-dummy design. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and all-cause serious adverse events (*Anderson et al 2015*).
 - Based on 4 studies in 2277 patients, the rate of exacerbations requiring oral corticosteroids was lower in patients taking a LAMA add-on than in those receiving the same dose of ICS alone (OR, 0.65; 95% CI, 0.46 to 0.93; $I^2 = 0\%$).
 - Based on 3 studies in 1713 patients, scores on the AQLQ were slightly higher for those taking a LAMA add-on compared to ICS alone (MD, 0.05; 95% CI, -0.03 to 0.12; $I^2 = 0\%$), but the difference was not statistically significant and was less than the established minimal clinically important difference of 0.5.

- Based on 5 studies in 2,562 participants, patients taking a LAMA reported fewer serious adverse events, but the effect was too inconsistent and imprecise to suggest a definite benefit over an ICS alone (OR, 0.6; 95% CI, 0.23 to 1.57; $I^2 = 59\%$).
- Benefits were also demonstrated with add-on LAMA therapy compared to ICS alone for the secondary endpoints including FEV₁ and PEF. Differences were not statistically significant for ACQ results or the number of exacerbations requiring hospitalization.
- A systematic review and meta-analysis compared the use of a LAMA vs a LABA when added to an ICS in patients with asthma. A total of 7 trials were included in the narrative review, and 4 of these trials (N = 2049) were included in the meta-analysis. All of the studies included in the meta-analysis used tiotropium as the LAMA and salmeterol as the LABA, and the duration of the trials ranged from 14 to 24 weeks. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and serious adverse events (*Kew et al 2015*).
 - Based on 3 studies in 1753 patients, there was no significant difference in the rate of exacerbations requiring oral corticosteroids between the LAMA and LABA groups (OR, 1.05; 95% CI, 0.50 to 2.18).
 - Based on 4 studies in 1,745 patients, those treated with a LAMA scored slightly worse than those treated with a LABA for quality of life measured on the AQLQ (MD, -0.12; 95% CI, -0.18 to -0.05). The difference was statistically significant, but both results fell below the established minimal clinically important difference of 0.5.
 - There was no difference detected in the rate of serious adverse events (OR, 0.84; 95% CI, 0.41 to 1.73); however, the rate of serious adverse events was too low for this result to be considered reliable.
 - Secondary endpoints showed little or no difference between the LAMA and LABA groups; these included FEV₁, PEF, FVC, exacerbations requiring hospitalization, and ACQ results.
- A systematic review and meta-analysis evaluated the addition of a LAMA to adults with asthma not well controlled by an ICS/LABA. Three double-blind trials (total N = 1197) comparing LAMA to placebo were included, and all trials evaluated tiotropium (mostly 5 mcg once daily via Respimat) (*Kew et al 2016*).
 - Based on 2 studies enrolling 907 patients, it was found that patients taking tiotropium plus an ICS/LABA had numerically fewer exacerbations requiring oral corticosteroids than those taking an ICS/LABA alone, but the confidence intervals did not rule out lack of a difference (OR, 0.75; 95% CI, 0.57 to 1.07). No benefit on quality of life was seen with the addition of tiotropium, based on results from the AQLQ (MD, 0.09; 95% CI, -0.03 to 0.20).
 - Secondary endpoints demonstrated a benefit on lung function, but no significant improvement in exacerbations requiring hospital admission or scores on asthma control measured by the ACQ.
- A meta-analysis of 4 randomized controlled trials evaluated tiotropium when added to low- to medium-dose ICS in adults with moderate uncontrolled asthma and found significant improvement with tiotropium in FEV percent predicted (3.46%; 95% CI, 2.20 to 4.63), peak FEV₁ (146.85 mL; (114.89 to 178.82)), trough FEV₁ (122.03 mL; 95% CI, 92.92 to 151.13). These results were consistent among subgroups treated with different doses of tiotropium (*Wang et al 2018*).

CLINICAL GUIDELINES

COPD

- The 2019 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2019*):
 - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms.
 - Inhaled bronchodilators are recommended over oral bronchodilators.
 - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
 - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
 - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
 - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
 - Combination treatment with a LABA and LAMA:
 - Reduces exacerbations compared to monotherapy or ICS/LABA.
 - Increases FEV₁ and reduces symptoms compared to monotherapy.
 - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.

- Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
 - **Group A:** Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
 - **Group B:** Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
 - **Group C:** Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/ μ L, ICS + LABA is preferred.
 - **Group D:** In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/ μ L. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
≥ 2 moderate severity (or ≥ 1 leading to hospital admission)	C	D
0 or 1 moderate severity (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but do not state that any combination is superior to LAMA monotherapy in patients with stable COPD (Criner *et al* 2015).

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (NHLBI 2007).
 - Ipratropium provides additive benefit to a SABA in moderate-to-severe asthma exacerbations, and may be used as an alternative bronchodilator for patients who do not tolerate a SABA.
 - The guideline states that ipratropium and tiotropium have not demonstrated effectiveness in the long-term management of asthma; however, it should be noted that this guideline has not been updated since 2007.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred initial controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom

severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, anti-IgE, anti-IL-5, **anti-IL-5 receptor, or anti-IL-4 receptor**) (*GINA 2018, GINA 2019a, GINA 2019b*).

- Tiotropium by mist inhaler is recommended as an add-on controller option in patients at higher steps (4 and 5). At step 4, it is recommended under “other controller options” (not preferred), and at step 5, it is recommended as one of several preferred add-on treatment options. In this setting, tiotropium is recommended as an add-on treatment for patients with a history of exacerbations; however, the guideline states that tiotropium is not for use in children younger than **6** years of age.
- Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation.
- A guideline on the definition, evaluation, and treatment of severe asthma is available from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (*Chung et al 2014*).
 - The guideline notes that ipratropium is commonly used in severe asthma patients in an attempt to reduce the daily use of beta₂-agonists, as well as in the treatment of asthma exacerbations. Although considered to be less effective, ipratropium is well tolerated and may be used alternately with beta₂-agonists for as-needed use throughout the day.
 - Tiotropium has been shown to improve lung function and symptoms in moderate-to-severe asthma patients not controlled on a moderate- to high-dose ICS with or without a LABA. In patients taking high doses of an ICS and a LABA, the addition of tiotropium has provided improvements in FEV₁, reduced as-needed SABA use, and modestly reduced the risk of a severe exacerbation. However, there have been no studies of tiotropium in children with asthma.
- A guideline on strategies for how and when to step down asthma therapies is available from the American College of Allergy, Asthma & Immunology (*Chippes et al 2019*).
 - For patients on step 4 therapy who are controlled on an ICS/LABA with tiotropium, the recommended first step in the step-down strategy is discontinuing tiotropium and continuing the ICS/LABA.
 - For patients on step 5 therapy, step down therapy should be approached more cautiously, but may be considered in select patients with at least 6 to 12 months of control with no exacerbations. The priority of step down in these patients is to taper oral corticosteroids. Other strategies in the guideline focus on biologic therapies in step 5 and tiotropium is not addressed for this specific population, likely due the complicated nature of treatment in patients with severe asthma.

SAFETY SUMMARY

- Ipratropium solution and Atrovent HFA are contraindicated in patients with hypersensitivity to ipratropium, atropine and its derivatives, or components of the product. Incruse Ellipta and Tudorza Pressair are contraindicated in patients with severe hypersensitivity to milk proteins or hypersensitivity to any ingredient. Seebri Neohaler and Lonhala Magnair are contraindicated in patients with known hypersensitivity to glycopyrrolate or any of the product ingredients. Spiriva Handihaler and Spiriva Respimat are contraindicated in patients with hypersensitivity to tiotropium, ipratropium, or components of the product. Yupelri (revefenacin) is contraindicated in patients with hypersensitivity to revefenacin or components of the product.
- Key warnings and precautions are similar among the anticholinergics, and include hypersensitivity, paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. It should also be noted that anticholinergics are for maintenance treatment and are not for initial treatment of acute episodes of bronchospasm where rescue therapy is required.
- The most common adverse effects reported for each anticholinergic are as follows:
 - Atrovent HFA (> 5% incidence): bronchitis, COPD exacerbation, dyspnea, and headache
 - Ipratropium solution (> 5% incidence): bronchitis, upper respiratory tract infection, dyspnea, and headache
 - Incruse Ellipta (≥ 2% incidence): nasopharyngitis, upper respiratory tract infection, cough, arthralgia
 - Lonhala Magnair (≥ 2% incidence): dyspnea and urinary tract infection
 - Seebri Neohaler (≥ 2% incidence): upper respiratory tract infection and nasopharyngitis
 - Spiriva Handihaler (> 5% incidence): upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis
 - Spiriva Respimat (> 3% incidence in COPD): pharyngitis, cough, dry mouth, and sinusitis;
Spiriva Respimat (> 2% incidence in asthma, adults): pharyngitis, sinusitis, bronchitis, and headache
 - Tudorza Pressair (> 5% incidence): headache, nasopharyngitis, and cough
 - Yupelri (≥ 2% incidence): cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain

- Although earlier trials raised some concerns about increased mortality with tiotropium when administered by the Respimat inhaler, a large, randomized, double-blind trial revealed no increased mortality for patients treated with tiotropium Respimat compared to tiotropium Handihaler (*Wise et al 2013*).
- Spiriva Handihaler, Tudorza, Incruse, and Seebri are Pregnancy Category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat, Lonhala Magnair, and Yupelri and are not currently assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

- Administration devices vary among products, and ease of use may vary based on patients' dexterity and coordination. Notably, Seebri Neohaler and Spiriva Handihaler require inserting individual capsules into the inhaler prior to each dose, and Spiriva Respimat requires coordination of inhalation with actuation of the device. The patient's ability to use an inhalation device is an important consideration in product selection.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atrovent HFA (ipratropium bromide)	Inhalation aerosol	Inhalation	Four times a day	<ul style="list-style-type: none"> • May use additional inhalations as required; maximum 12 inhalations per 24 hours • Canister-style inhaler; requires inserting the canister and priming before use • Hand/breath coordination is required
Incruse Ellipta (umeclidinium)	Inhalation powder	Inhalation	Once daily	<ul style="list-style-type: none"> • Disc-shaped inhaler with self-contained foil blister strips; opening the inhaler prepares a dose • Breath-activated; hand/breath coordination not required
ipratropium bromide solution	Inhalation solution	Inhalation (with nebulizer)	Three to 4 times per day	<ul style="list-style-type: none"> • May be mixed in nebulizer with albuterol or metaproterenol if used within 1 hour
Lonhala Magnair (glycopyrrolate)	Inhalation solution	Inhalation (with nebulizer)	Twice daily	<ul style="list-style-type: none"> • Lonhala should only be administered with the Magnair device. • Supplied in vials with complete Magnair nebulizer system (starter kit) or refill handset (refill kit) • 2 to 3 minutes to administer, plus cleaning/prep time
Seebri Neohaler (glycopyrrolate)	Inhalation powder	Inhalation	Twice daily	<ul style="list-style-type: none"> • Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Handihaler (tiotropium bromide)	Inhalation powder	Inhalation	Once daily	<ul style="list-style-type: none"> • Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Respimat (tiotropium bromide)	Inhalation spray	Inhalation	Once daily	<ul style="list-style-type: none"> • Inhaler should be primed before first use and if not used for > 3 days; if not used for > 21 days, inhaler should be actuated until an aerosol cloud is visible, and then the process should be repeated 3 more times to prepare the inhaler for use.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				<ul style="list-style-type: none"> • Maximum benefits in asthma treatment may take up to 4 to 8 weeks • Canister-style inhaler; requires inserting the canister and priming before use • Twisting the canister prepares a dose for inhalation • Hand/breath coordination is required
Tudorza Pressair (aclidinium bromide)	Inhalation powder	Inhalation	Twice daily	<ul style="list-style-type: none"> • Dry powder inhaler; pressing a button prepares a dose • Breath-activated; hand/breath coordination not required
Yupelri (revefenacin)	Inhalation solution	Inhalation (with nebulizer)	Once daily	<ul style="list-style-type: none"> • The safety and efficacy of revefenacin delivered from non-compressor based nebulizer systems have not been established. • Unit-dose vial should only be removed from the foil pouch and opened immediately before use. • Revefenacin should not be mixed with any other medications. • Treatment requires 8 minutes for administration, plus cleaning/prep time.

See the current prescribing information for full details.

CONCLUSION

- The respiratory anticholinergics are used predominantly for the management of COPD, with an additional asthma indication specific to Spiriva Respimat (tiotropium).
 - Short-acting respiratory anticholinergics include Atrovent HFA (ipratropium bromide) inhalation aerosol and ipratropium bromide solution for nebulization.
 - The LAMAs include 5 molecular entities in 7 formulations: Incruse Ellipta (umeclidinium) inhalation powder, Lonhala Magnair (glycopyrrolate) inhalation solution and Seebri Neohaler (glycopyrrolate) inhalation powder, Spiriva Handihaler (tiotropium) inhalation powder and Spiriva Respimat (tiotropium) inhalation spray, Tudorza Pressair (aclidinium) inhalation powder, and Yupelri (revefenacin) inhalation solution.
- All LAMAs are indicated for the long-term maintenance treatment of airflow obstruction in patients with COPD, while Spiriva Handihaler and Respimat are also indicated to reduce COPD exacerbations. Spiriva Respimat is additionally indicated for the maintenance treatment of asthma.
 - Spiriva Handihaler (tiotropium bromide), Spiriva Respimat (tiotropium bromide), Incruse Ellipta (umeclidinium), and Yupelri (revefenacin) are all administered once daily, while the Seebri Neohaler and Tudorza Pressair are administered twice daily.
 - Lonhala Magnair is administered twice daily via the Magnair nebulizer. This product is appropriate for a small percentage of COPD patients who are unable to effectively use other inhalation devices.
 - Devices and administration methods vary among products, and some may be favored over others for patients with dexterity issues, suboptimal peak inspiratory flow rate, and/or difficulty with coordinating actuation of the device with inhalation.
- Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy is well established through placebo-controlled trials and systematic reviews and meta-analyses. Improvement in lung function, health status and/or respiratory symptoms vs placebo has been demonstrated for all products.
 - Limited comparisons among LAMAs have been conducted. Some have demonstrated differences, particularly for the lung function endpoints (ie, FEV₁), but no clear differences in symptoms or other patient-reported outcomes.
 - Tiotropium and umeclidinium have evidence supporting a reduction in COPD exacerbations; however, only tiotropium is indicated to reduce exacerbations per FDA-approved labeling.

- Safety is comparable among products. Key warnings/precautions include paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. Spiriva Handihaler, Tudorza, Incruse, and Seebri are pregnancy category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat, Lonhala Magnair, and Yupelri (revefenacin) are not assigned a Pregnancy Category.
- GOLD guidelines recommend LAMAs for most patients with COPD, as they improve lung function, dyspnea, and health status, and reduce exacerbations.
 - There is no preference stated for one LAMA compared to another; however, the choice of agent should be based on an assessment of the patient's symptoms and risk of exacerbations.
 - LAMAs have a greater effect on exacerbation reduction compared to LABAs.
 - Guidelines emphasize that the use of long-acting bronchodilators is recommended over short-acting bronchodilators except for patients with only occasional dyspnea, and inhaled therapy is preferred.
- GINA guidelines recommend tiotropium Respimat be considered in patients ≥ 6 years of age whose asthma is not well controlled with an ICS/LABA combination.

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Publication Date: June 12, 2019

Daliresp (roflumilast)





Prior Authorization Guideline

Guideline Name Daliresp (roflumilast)

1 . Indications

Drug Name: Daliresp (roflumilast)

Indications

Chronic obstructive pulmonary disorder (COPD) Indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Limitations of Use: Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm. Daliresp 250 mcg is a starting dose, for the first 4 weeks of treatment only and is not the effective (therapeutic) dose.

2 . Criteria

Product Name: Daliresp

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

Approval Criteria

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

- a. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting anticholinergic agent;
- b. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting beta agonist;
- c. The recipient has experienced an inadequate response, adverse event or has a contraindication to an inhaled corticosteroid;

- d. The recipient has a diagnosis of severe Chronic Obstructive Pulmonary Disease (COPD) associated with chronic bronchitis; and
- e. The recipient has a history of COPD exacerbations.

Product Name: Daliresp

Approval Length	12 Month
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

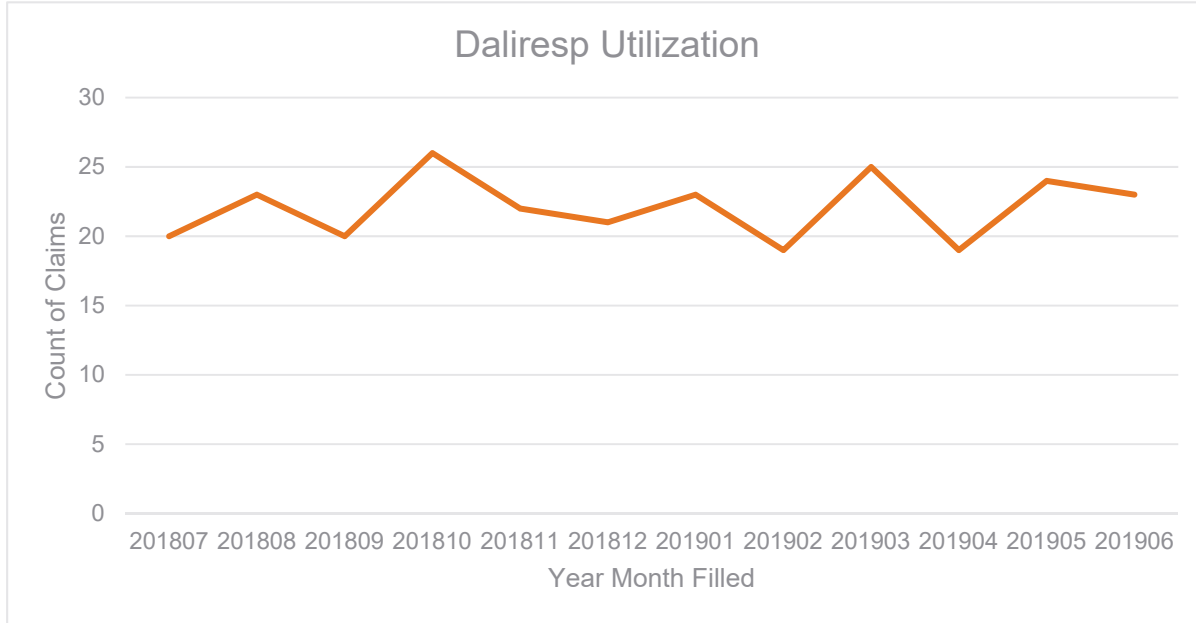
- a. Documentation of positive clinical response to Daliresp therapy

Daliresp Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
DALIRESP	44	265	8,081	8,081



II. Daliresp® (roflumilast)

Therapeutic Class: Phosphodiesterase-4 Inhibitors.

Last Reviewed by the DUR Board: July 26, 2012

Daliresp® (roflumilast) 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

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

- a. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting anticholinergic agent;
- b. The recipient has experienced an inadequate response, adverse event or has a contraindication to a long-acting beta (β) agonist;
- c. The recipient has experienced an inadequate response, adverse event or has a contraindication to an inhaled corticosteroid;
- d. The recipient has a diagnosis of severe Chronic Obstructive Pulmonary Disease (COPD) associated with chronic bronchitis; and
- e. The recipient has a history of COPD exacerbations.

2. Prior Authorization Guidelines

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

Therapeutic Class Overview

Phosphodiesterase-4 inhibitor for COPD

INTRODUCTION

- Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is persistent and usually progressive. There are several pathologic mechanisms underlying the airflow limitation, including airway inflammation and fibrosis, luminal plugs, increased airway resistance, parenchymal destruction, loss of alveolar attachments, and decrease of elastic recoil. Exacerbations and comorbidities contribute to the severity of COPD (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018*).
- COPD affects more than 5% of the adult population and is the third leading cause of death in the United States. In addition, COPD is the twelfth leading cause of morbidity in the United States (*Qaseem et al 2011*).
- Cigarette smoking is a primary risk factor for COPD. Approximately 85 to 90% of COPD cases are caused by smoking. Other risk factors include heredity, air pollution exposure, second-hand smoke, occupational dust and chemicals, and a history of childhood respiratory infections (*American Lung Association [ALA] 2019*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2018*).
- Daliresp (roflumilast) is an oral selective phosphodiesterase (PDE)-4 inhibitor that is Food and Drug Administration (FDA)-approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
- The GOLD guidelines state that roflumilast is an alternative (not first-choice) addition to the treatment regimen of selected patients who are not adequately controlled by their current therapy (*GOLD 2018*).
- Roflumilast is the only FDA-approved medication in the PDE-4 inhibitor category with a respiratory indication, and thus the only medication included in this review.
- Medispan class: Anti-asthmatic and Bronchodilator agents, Selective PDE-4 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daliresp (roflumilast)	-*

* Generic roflumilast has been FDA approved but is not yet commercially available

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

INDICATIONS

- Roflumilast is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
 - Limitations of use:
 - Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
 - Roflumilast 250 mcg is a starting dose used only for the first 4 weeks of treatment and is not the effective (therapeutic) dose.

(*Daliresp prescribing information 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

- Roflumilast has been evaluated in a number of placebo-controlled clinical trials. In some trials, concomitant treatment with a long-acting bronchodilator was permitted or required (in agreement with the GOLD guidelines) (*Bateman et al 2011, Calverley et al 2009, Fabbri et al 2009*). In other studies, concurrent therapy with only short-acting bronchodilators

Data as of June 13, 2019 JD/KAL

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with or without inhaled corticosteroids (ICS) was permitted (*Calverley et al 2007, Lee et al 2011, O'Donnell et al 2012, Rabe et al 2005, Rennard et al 2011*). Roflumilast has not been directly compared to other active agents for the treatment of COPD.

- In a trial conducted by *Rabe et al*, 1411 patients with moderate to severe COPD were randomized to treatment with roflumilast 250 or 500 mcg/day or placebo for 6 months. Concurrent COPD medications allowed were short-acting β -agonists (SABAs) as rescue therapy and short-acting anticholinergics at a constant daily dose. After 6 months, patients treated with roflumilast achieved significant improvements in post-bronchodilator forced expiratory volume in 1 second (FEV₁) compared to baseline ($p < 0.05$ for both doses) and compared to patients treated with placebo ($p < 0.03$ for both doses). Improvements from baseline Saint George's Respiratory Questionnaire (SGRQ) scores were also significant for both doses of roflumilast ($p < 0.001$ and $p < 0.0001$), but not when compared to placebo ($p = 0.053$ and $p = 0.077$). As for the secondary endpoints evaluated, roflumilast was associated with significant reductions in acute COPD exacerbations compared to treatment with placebo ($p = 0.0029$); the greatest effect was a 34% reduction with the 500 mcg dose compared to placebo (*Rabe et al 2005*).
- In another placebo-controlled trial conducted by *Calverley et al*, patients with moderate to severe COPD were randomized to roflumilast 500 mcg daily or placebo for 1 year. In this trial, concurrent COPD medications allowed were SABA as rescue therapy, short-acting anticholinergics, and ICS (≤ 2000 mcg beclomethasone or equivalent). Again, patients treated with roflumilast achieved significant improvements in post-bronchodilator FEV₁ compared to placebo-treated patients ($p < 0.001$). In this trial, however, the rate of moderate or severe COPD exacerbations, a co-primary endpoint, was not significantly different between roflumilast- and placebo-treated patients (0.86 vs 0.92 per patient per year; p value not reported). A post-hoc analysis of the data revealed that COPD exacerbations were more frequent in GOLD Stage IV COPD patients. Within this group, exacerbations were significantly less frequent among those treated with roflumilast compared to those treated with placebo ($p = 0.024$). Changes in SGRQ scores were again evaluated as a secondary endpoint but were found to not differ between treatment groups ($p = 0.086$) (*Calverley et al 2007*).
- *Rennard et al* pooled the results from *Calverley et al* with an identical, 1-year, placebo-controlled trial, both of which were inconclusive regarding the effect of roflumilast on exacerbations. Improvements in pre- and post-bronchodilator FEV₁, the primary and secondary endpoint, were again significantly greater among roflumilast-treated patients compared to placebo-treated patients. In the pooled analysis, treatment with roflumilast was associated with a 14.3% lower rate (0.52 vs 0.61 per year) of moderate to severe exacerbations (co-primary endpoint) compared to treatment with placebo ($p = 0.026$) (*Rennard et al 2011*).
- Two additional, identical, 1-year, placebo-controlled trials conducted by *Calverley et al* evaluated the effects of roflumilast on pre-bronchodilator FEV₁ values as a co-primary endpoint, along with the rate of moderate or severe acute exacerbations. These trials allowed concurrent use of long-acting β -agonists (LABAs), in addition to SABAs as rescue therapy and short-acting anticholinergics. At the end of 1 year, pooled analysis revealed that patients treated with roflumilast achieved significant improvements in pre-bronchodilator FEV₁ ($p < 0.0001$) and had a significantly lower rate of moderate or severe acute exacerbations (relative risk [RR], 0.83; 95% confidence interval [CI], 0.75 to 0.95; $p = 0.0003$) compared to patients treated with placebo. Of the secondary outcomes evaluated, only the pooled Transition Dyspnea Index (TDI) focal scores were significantly improved in roflumilast-treated patients compared to placebo-treated patients ($p = 0.0009$). Mortality rates (p values not reported) and time to mortality did not differ between treatment groups (206.1 vs 211.7 days; hazard ratio, 1.1; 95% CI, 0.7 to 1.8; $p = 0.5452$) (*Calverley et al 2009*).
- A similar 12-week study compared roflumilast 500 mcg daily to placebo in 411 Asian patients with COPD. Patients were allowed salbutamol as rescue medication and short-acting anticholinergics at a constant daily dosage; however, other medications including LABAs and long-acting anticholinergics were not allowed. Similar to other trials, the primary outcome, change in post-bronchodilator FEV₁, was significantly improved in the roflumilast group (+52 mL, 95% CI, 13 to 91) compared to the placebo group (-27 mL, 95% CI, -66 to 12). No improvement in the secondary outcome of COPD exacerbations was noted in the roflumilast group compared to the placebo group; however, the study was not powered to detect these differences (*Lee et al 2011*).
- A 24-week study, also in Asian patients, compared roflumilast 500 mcg daily to placebo in 626 patients with COPD. Patients were permitted to continue taking fixed combinations of ICS/LABA, or short- or long-acting muscarinic antagonists (LAMA) at a stable dose, as well as rescue medication (product and dose not specified). Results demonstrated an improvement in the primary endpoint, change in FEV₁, with an increase in the roflumilast group (0.049 L; 95% CI, 0.032 to 0.066) and a decrease in the placebo group (-0.022 L; 95% CI, -0.039 to -0.005). The difference of 0.071 L was statistically significant ($p < 0.0001$). Other lung function endpoints were also significantly improved with

roflumilast. However, no improvement in several secondary endpoints, including the exacerbation rate, use of rescue medication, or TDI score, was observed (*Zheng et al 2014*).

- *Bateman et al* reported results of 2 double-blind, multicenter, randomized controlled trials (RCTs) comparing roflumilast to placebo in patients with COPD. Concomitant respiratory medications permitted during the trial were SABAs as rescue medication, LABAs, and short-acting anticholinergics at stable doses. Results demonstrated that roflumilast led to improvements in pre-bronchodilator and post-bronchodilator FEV₁, as well as the rate of exacerbations per year. The reduction in exacerbations was similar in patients with and without concomitant LABA use (*Bateman et al 2011*).
- A study conducted by *O'Donnell et al* evaluated the effects of roflumilast on airway physiology during rest and exercise in 250 patients with COPD in a 12-week, placebo-controlled trial. Patients were allowed salbutamol as rescue medication, ipratropium at a constant daily dosage, and ICS at a constant daily dosage; other medications were not permitted. Results demonstrated no significant treatment difference in the primary endpoint, exercise endurance time. For secondary endpoints, small changes in airway function were observed, including those for pre- and post-bronchodilator FEV₁ and FEV₁/forced vital capacity (FVC). Additionally, small improvements in selected physiologic endpoints were noted during exercise, including ventilation at peak exercise and arterial oxygen saturation. The clinical significance of these physiologic changes requires further study (*O'Donnell et al 2012*).
- *Fabbri et al* reported results of 2 double-blind, multicenter, placebo-controlled trials. In Trial 1 (n = 935), roflumilast 500 mcg daily was given concomitantly with salmeterol, and in Trial 2 (n = 744), it was given concomitantly with tiotropium. Both trials demonstrated improvements in pre-bronchodilator and post-bronchodilator FEV₁, and post-bronchodilator FVC with roflumilast. However, the rate of mild, moderate, or severe COPD exacerbations was not significantly reduced with roflumilast in either trial (*Fabbri et al 2009*).
- *Martinez et al* reported results of a double-blind, multicenter, placebo-controlled trial (N = 1945) that enrolled COPD patients with severe airflow limitation (FEV₁/FVC < 0.7 and post-bronchodilator FEV₁ ≤ 50% predicted) and a history of ≥ 2 exacerbations in the previous year. Patients must have been taking a combination ICS/LABA for ≥ 12 months with a stable dose for ≥ 3 months. Concomitant tiotropium was allowed but not required. Patients were randomized to receive roflumilast 500 mcg daily or placebo for 52 weeks. The primary endpoint, the rate of moderate-to-severe COPD exacerbations per patient per year, was 0.805 with roflumilast and 0.927 with placebo (RR, 0.868; 95% CI, 0.753 to 1.002; p = 0.0529) according to the Poisson regression analysis. Results were similar using a different type of statistical analysis, negative binomial regression, and with this method results were statistically significant (p = 0.0424). Roflumilast reduced the incidence of severe exacerbations (RR, 0.757; p = 0.0175) and exacerbations necessitating hospital admission (RR, 0.761; p = 0.0209). Roflumilast treatment also improved FEV₁ and FVC, with differences from placebo of 56 mL and 92 mL, respectively (p < 0.0001 for both comparisons). Although results on the primary endpoint were of borderline statistical significance, this study demonstrates some benefit with roflumilast in this high-risk group of patients who were concomitantly treated with ICS/LABA (*Martinez et al 2015*).
- A meta-analysis reported pooled data from 4 placebo-controlled RCTs (total N = 5595) to evaluate the effects of roflumilast on dyspnea in patients with moderate to very severe COPD. The meta-analysis demonstrated that at week 52, roflumilast significantly improved the mean TDI focal score, with a difference of 0.327 units (95% CI, 0.166 to 0.488; p < 0.0001). This mean change was less than the minimum clinically important difference of 1 unit. However, the authors report that the percentage of TDI responders (≥ 1 unit) was greater in patients treated with roflumilast (39%) than in patients treated with placebo (33.9%) (p < 0.01) (*Rennard et al 2014*).
- A meta-analysis of 26 RCTs evaluated the roles of LABA, long-acting anticholinergics, ICS, and roflumilast therapy, both alone and in combination, on the rate of COPD exacerbations. The primary endpoint was reported in terms of an absolute treatment effect, expressed as mean exacerbations experienced per patient per year. A regimen composed of roflumilast, LABA, long-acting anticholinergics, and an ICS was associated with the greatest reduction in the number of exacerbations (absolute treatment effect, 0.53; 95% CI, 0.43 to 0.64). In comparison, the treatment effect of roflumilast monotherapy was 1.01 (95% CI, 0.89 to 1.14). A combination of long-acting anticholinergic, LABA and ICS therapies was associated with a treatment effect of 0.63 (95% CI, 0.54 to 0.73) (*Mills et al 2011*). A smaller meta-analysis of 8 clinical trials found that roflumilast reduced the overall rate of exacerbations compared to placebo (-0.41 events/patient-year; 95% CI, -0.72 to -0.11) (*Oba and Lone 2013*).
- A Cochrane systematic review reported a significant improvement in pulmonary function with roflumilast therapy. The review of PDE-4 inhibitors for COPD found small improvements in quality of life and COPD-related symptoms, but not exercise tolerance. An evaluation of 23 trials (N = 19,948) showed that treatment with PDE-4 inhibitors was associated with a reduced likelihood of COPD exacerbation (odds ratio [OR] 0.78; 95% CI, 0.73 to 0.83). Roflumilast was associated with diarrhea, weight loss, increased insomnia, and depressive mood symptoms (*Chong et al 2017*).

- In the 52-week, multicenter, randomized, double-blind, placebo-controlled RE²SPOND trial, patients with severe to very severe COPD, chronic bronchitis, 2 or more exacerbations in the previous year, and on standard ICS/LABA with or without LAMA therapy were randomized to receive roflumilast (n = 1178) or placebo (n = 1176). The primary endpoint, reduction in moderate and/or severe exacerbations, was not found to be statistically significant (95% CI, 0.81 to 1.04; p = 0.163). Roflumilast was, however, shown to improve FEV₁ from baseline (p < 0.0001) as similarly demonstrated by previous studies. Post hoc analysis demonstrated a statistically significant reduction of moderate to severe exacerbations in the subset of patients with a history of higher exacerbation burden (> 3 exacerbations per year) and hospitalization, suggesting roflumilast may have a place in therapy for this demographic (*Martinez et al 2016*).
- The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation (*GOLD 2018, Rabe et al 2017*).
- There has been no study directly comparing roflumilast with an ICS (*GOLD 2018*).

CLINICAL GUIDELINES

- Treatment guidelines for COPD include:
 - Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (*GOLD 2018*)
 - Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS) (*Qaseem et al 2011*)
 - Institute for Clinical Systems Improvement (ICSI): Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD) (*Anderson et al 2016*)
 - American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS): Prevention of Acute Exacerbations of COPD (*Criner et al 2015*)
- In the GOLD guidelines, treatment strategies are based on a combination of a patient's symptoms and impairment as determined by the COPD Assessment Test (CAT) or Modified British Medical Research Council (mMRC) Questionnaire, spirometry results, and exacerbation history. The guidelines note that in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations, roflumilast may be added to therapy to improve lung function and reduce moderate and severe exacerbations. Roflumilast may also improve lung function and reduce exacerbations in patients not well-controlled on fixed-dose LABA/ICS combinations. First-choice recommendations in the GOLD guidelines are as follows:
 - **Group A** (0 to 1 exacerbations not leading to hospital admission, CAT < 10/mMRC 0 to 1): short or long-acting bronchodilator as needed
 - **Group B** (0 to 1 exacerbations not leading to hospital admission, CAT ≥ 10/mMRC ≥ 2): long-acting bronchodilator (LABA or LAMA); may progress to LAMA + LABA if symptoms persist
 - **Group C** (≥ 2 exacerbations or ≥ 1 leading to hospital admission, CAT < 10/mMRC 0 to 1): LAMA; may progress to LAMA + LABA (preferred) or LABA + ICS for persistent exacerbations
 - **Group D** (≥ 2 exacerbations or ≥ 1 leading to hospital admission, CAT ≥ 10/mMRC ≥ 2): LAMA + LABA; may progress to LAMA + LABA + ICS for persistent exacerbations; if exacerbations persist, may add roflumilast for patients with an FEV₁ < 50% predicted and chronic bronchitis, or a macrolide for former smokers (*GOLD 2018*)
- The ACP/ACCP/ATS/ERS guidelines do not include information or recommendations about roflumilast. Key recommendations in this guideline include:
 - For symptomatic patients with COPD and FEV₁ < 60% predicted, it is recommended that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or LABAs (strong recommendation, moderate-quality evidence). For this group of patients, it is suggested that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, LABAs, or ICS) (weak recommendation, moderate-quality evidence) (*Qaseem et al 2011*).
- The ICSI guidelines recommend against roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. The guidelines note that roflumilast leads to a modest improvement in airflow and a reduction in exacerbations, and patients most likely to benefit are those with a history of frequent exacerbations, chronic bronchitis, cough, and sputum production (*Anderson et al 2016*).
- The ACCP/CTS guidelines suggest the use of roflumilast to prevent acute exacerbations of COPD in patients with moderate to severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the previous year (*Criner et al 2015*).

SAFETY SUMMARY

- Roflumilast is contraindicated in moderate to severe liver impairment (Child-Pugh B or C).
- Warnings and precautions include the following:
 - Roflumilast is not a bronchodilator and should not be used for the relief of acute bronchospasm.
 - Psychiatric events including suicidality: Treatment is associated with an increase in psychiatric adverse reactions, including insomnia, anxiety, and depression. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials with roflumilast in patients with and without a history of depression.
 - Prescribers should carefully weigh risks and benefits of treatment with roflumilast before using in patients with a history of depression and/or suicidal thoughts or behavior. Patients, caregivers, and families should be advised of the need to be alert for psychiatric adverse events.
 - An analysis of FDA Adverse Event Reporting System (FAERS) reports conducted by the Institute for Safe Medication Practices (ISMP) and published in April 2017 identified a confirming signal for suicidal and self-injurious behaviors (*ISMP 2017*).
 - Weight decrease: Weight loss may occur with roflumilast use.
 - Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and discontinuation of roflumilast should be considered.
- Drug Interactions include the following:
 - Strong cytochrome P (CYP) 450 enzyme inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampicin) decrease systemic exposure to roflumilast and may reduce its therapeutic effectiveness; concurrent use is not recommended.
 - Concurrent administration of roflumilast with CYP3A4 inhibitors or dual inhibitors that inhibit CYP3A4 and 1A2 simultaneously (eg, cimetidine, enoxacin [not available in the U.S.], erythromycin, fluvoxamine, ketoconazole) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of concurrent use should be weighed carefully against benefit.
 - The concurrent administration of roflumilast and oral contraceptives containing gestodene (not available in U.S.) and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased adverse effects. The risk of such concurrent use should be weighed carefully against benefit.
- Common adverse events (incidence \geq 2%) include diarrhea, weight loss, headache, nausea, back pain, insomnia, influenza, dizziness, and decreased appetite.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Daliresp (roflumilast)	Tablets	Oral	Once daily	May be taken with or without food.

See the current prescribing information for full details

CONCLUSION

- Roflumilast is a once-daily, orally administered PDE-4 inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The agent is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
- Some (but not all) RCTs have demonstrated the ability of roflumilast to reduce exacerbations in patients at high risk of exacerbations (*Bateman et al 2011, Calverley et al 2009, Martinez et al 2015*). Roflumilast does not replace bronchodilators, but it is used adjunctively in appropriate patients.
- The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation (*GOLD 2018, Rabe et al 2017*).
- Roflumilast is generally well tolerated, with the most frequent adverse events being diarrhea, nausea, and headache. Roflumilast has also been associated with psychiatric events including suicidality. Roflumilast should be used with caution in patients with depression. Potential drug interactions and weight loss are also considerations.

- The GOLD treatment guideline positions PDE-4 inhibitors as additional therapeutic agents for patients with COPD exacerbations despite long-acting bronchodilator therapy, particularly if they have experienced at least 1 hospitalization for an exacerbation in the previous year. It is acknowledged that PDE-4 inhibitors have more adverse events than inhaled medications for COPD including nausea, reduced appetite, weight loss, abdominal pain, diarrhea, sleep disturbance, and headache; however, adverse events seem to occur early and diminish over time (*GOLD 2018*). The ICSI guideline states that the exact place in treatment for roflumilast is not defined (*Anderson et al 2016*). A guideline from ACCP/CTS suggests the use of roflumilast to prevent acute exacerbations of COPD in patients with moderate to severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the previous year (*Criner et al 2015*).
- Although not a first-line agent, roflumilast is unique because it is the only medication in the PDE-4 inhibitor class indicated for management of COPD. It is included in clinical guidelines and has a role in the treatment of appropriately selected patients with COPD.

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Publication Date: June 24, 2019

Topical Antiparasitics





Prior Authorization Guideline

Guideline Name Natroba (spinosad)

1 . Criteria

Product Name: Natroba (spinosad)

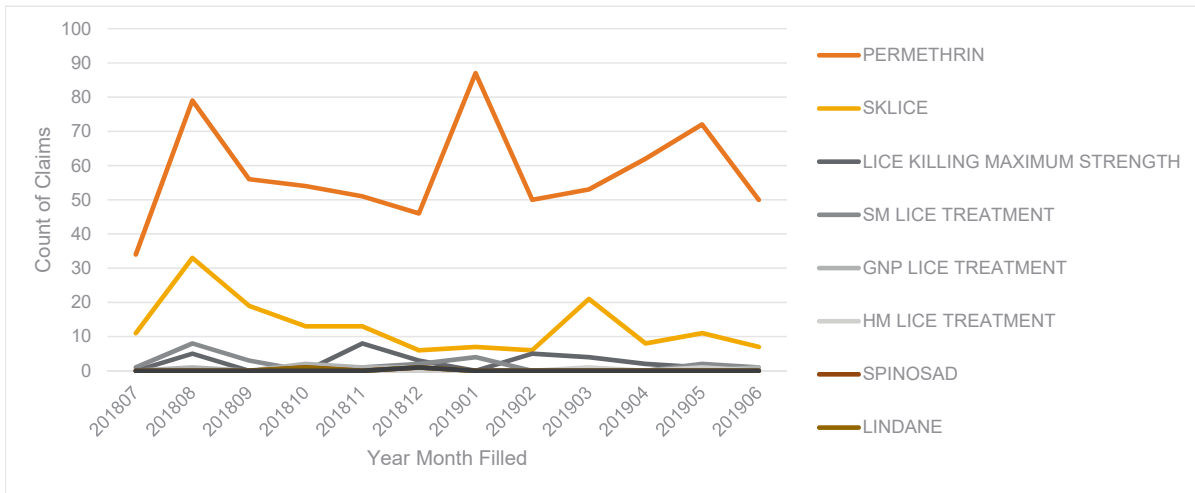
Guideline Type	Prior Authorization
Coverage and Limitations	
Authorization will be given if the following criteria are met and documented:	
<ul style="list-style-type: none">a. The recipient has experienced an allergy or adverse event with a permethrin or pyrethrin-containing pediculicide product; orb. The recipient has experienced a treatment failure with a permethrin or pyrethrin-containing pediculicide product despite a full course of treatment (two applications); orc. The recipient has a contraindication to treatment with permethrin or pyrethrin-containing pediculicide product.	

Topical Antiparasitics Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
GNP LICE TREATMENT	5	6	30	413
HM LICE TREATMENT	1	3	48	180
LICE KILLING MAXIMUM STRENGTH	16	28	133	3,599
LINDANE	1	2	60	120
PERMETHRIN	461	694	5,358	48,333
SKLICE	112	155	1,313	20,241
SM LICE KILLING MAXIMUM STRENGTH	1	1	1	118
SM LICE TREATMENT	17	22	142	1,534
SPINOSAD	1	2	60	240



MM. Natroba® (spinosad)

Therapeutic Class: Topical Antiparasitics

Last Reviewed by the DUR Board: July 26, 2012

Natroba® (spinosad) is subject to prior authorization.

1. Coverage and Limitations

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

- a. The recipient has experienced an allergy or adverse event with a permethrin or pyrethrin-containing pediculicide product; or
- b. The recipient has experienced a treatment failure with a permethrin or pyrethrin-containing pediculicide product despite a full course of treatment (two applications); or
- c. The recipient has a contraindication to treatment with permethrin or pyrethrin-containing pediculicide product.

2. Prior Authorization Guidelines

- a. Prior authorization approval will be for the date of service only.
- b. Prior Authorization forms are available at:
<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

INTRODUCTION

- Scabies and pediculosis are infestations of the skin caused by ectoparasites. Scabies is caused by the parasitic mite *Sarcoptes scabiei* and often results in an intense pruritic eruption and itching. Pediculi or lice can cause infestations either on the head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), or the pubic region (*Phthirus pubis*). These skin conditions are common causes of skin rash and pruritus (Roos *et al* 2001, Wendel *et al* 2002). Head lice infestation crosses all social and geographic boundaries and generally affects children, primarily females, aged three to 12 years (Feldmeier 2012). Scabies occur in both sexes, at all ages, and in all ethnic and socioeconomic groups; however, one epidemiologic study reported a higher prevalence in urban areas among women and children (Chosidow 2006, Downs *et al* 1999). The ideal agent for the treatment of head lice is one with high pediculicidal (capable of killing lice) and ovicidal (capable of killing eggs) activity with minimal toxicity (Villegas *et al* 2012).
- The topical agents indicated for the management of scabies and head lice are listed in Table 1. All of the agents included in this review are Food and Drug Administration (FDA)-approved for the treatment of head lice with the exception of Eurax (crotamiton), which is only indicated to treat scabies. Lindane lotion indicated to treat scabies has been discontinued; the shampoo is still available for the treatment of lice.
- The pediculicidal effects of most of these agents result from their neurotoxic effects on lice. These agents, except benzyl alcohol, cause periods of central nervous system hyperexcitation, resulting in paralysis and ultimately death of the lice. Ulesfia (benzyl alcohol) is unique in that it disables the breathing structure of the lice, resulting in asphyxiation rather than neuroexcitation. Neurotoxic insecticides rely on the nervous system to exert their effect; therefore, newborn larvae are not susceptible to these agents since they do not develop a nervous system for several days after hatching. This presents a challenge for eliminating lice with a single treatment because the infestation typically includes lice from all stages of the life cycle, including newly hatched eggs.
- RID (piperonyl butoxide, pyrethrum extract) and NIX (permethrin) are pediculicidal, but not ovicidal, and therefore require nit combing and retreatment in 7 to 10 days to eradicate the infestation. Benzyl alcohol is not ovicidal and also requires a second treatment, but resistance is unlikely due to its unique mechanism of action. Malathion is both pediculicidal and ovicidal, but it is malodorous, requires 8 to 12 hours of application and is highly flammable. Lindane is neurotoxic and is not recommended as an initial treatment option. Sklice (ivermectin) and Natroba (spinosad) are pediculicidal but not ovicidal. Topical ivermectin is approved as a single application product only.
- Some data suggest a growing resistance to permethrin in the United States, with recent studies stating that the effectiveness of permethrin has declined to 25% and resistance to pyrethrins is widespread (Koch *et al* 2016, *The Medical Letter* 2016). However, both the United States Centers for Disease Control and Prevention (CDC) as well as the American Academy of Pediatrics (AAP) continue to recommend permethrin as first-line therapy for treatment of both lice and scabies. Permethrin 1% or pyrethrins should be used when resistance is not suspected. Malathion (in patients who are 6 years of age or older) and benzyl alcohol (in children older than 6 months) are available as alternative agents if the first-line medications are inappropriate or ineffective. Spinosad and ivermectin might prove helpful in difficult cases, but are more costly. Lindane is no longer recommended for use as treatment of head lice (AAP Red Book 2018, CDC 2015[a], CDC 2015[b], CDC 2016, CDC 2018, Devore *et al* 2015, Downs *et al* 1999).
- Medispan class: Scabicides and pediculicides and scabicide combinations.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Eurax (crotamiton cream and lotion)	✓ ‡
Lindane (gamma-hexachlorocyclohexane)*	✓
Natroba (spinosad)	✓
Ovide (malathion)	✓
Permethrin (Elimite 5%, NIX 1% lice treatment†)	✓
Piperonyl butoxide and pyrethrins (RID†)	✓
Sklice (ivermectin)**	-
Ulesfia (benzyl alcohol)	-

†Over-the-counter (OTC) product is available in at least one dosage form or strength. Not all product options are listed as there are a number of OTC products available.

‡Generic Crotan (crotamiton lotion) is available; the cream is brand only.

*Lindane shampoo is available; the lotion formulation has been discontinued.

**Another product, trade name Soolantra, is available as a 1% cream and is indicated for rosacea.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Eurax (crotamiton)	Lindane (gamma-hexachlorocyclohexane)	Natroba (spinosad)	Ovide (malathion)	Permethrin (Elimite, NIX)	Piperonyl butoxide and pyrethrins (RID)	Sklice (ivermectin)	Ulesfia (benzyl alcohol)
Scabies	✓				✓ §#			
Head lice		✓ *	✓ ‡	✓ †	✓ #	✓ ¶	✓ ‡	✓ ‡
Pubic (crab) lice		✓ *				✓ ¶		
Body lice						✓ ¶		

*Lindane shampoo is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head or pubic lice.

† In patients ≥ 6 years of age

‡ In patients ≥ 6 months of age

§ Permethrin 5% cream is indicated for the treatment of scabies.

|| Permethrin 1% lotion/cream rinse is indicated for the treatment of head lice.

In patients ≥ 2 months of age

¶ In patients ≥ 2 years of age

(Clinical Pharmacology 2019; Prescribing information: Elimite 2015, Eurax 2012, Lindane 2009, Natroba 2014, Ovide 2017, Sklice 2017, Ulesfia 2015)

- 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

Scabies

Data as of Feb 1, 2019 RS-U/RR-U/AVD

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- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and Lindane (*Amer et al 1992, Haustein et al 1989, Schultz et al 1990, Taplin et al 1986b, Taplin et al 1990, Zargari et al 2006*). In the largest study (N = 467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin compared to Lindane; however, the difference was not statistically significant (*Schultz et al 1990*). In a single-blind, randomized controlled trial comparing ivermectin to crotamiton (N = 340), 2 applications of ivermectin were as effective as a single application of crotamiton cream for the treatment of scabies at 2 weeks. After repeating therapy, ivermectin was superior to crotamiton cream at 4 weeks follow-up (*Goldust et al 2014*).
- Both Lindane and permethrin have also been compared to oral ivermectin for the treatment of scabies. Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with Lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*). However, another study found similar efficacy between the 2 agents at days 15 and 29 after treatment (*Chouela et al 1999*). Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (*Usha et al 2000*).
- A Cochrane review evaluated 15 studies comparing topical permethrin, topical ivermectin, and oral ivermectin for scabies (*Rosumeck et al 2018*). The meta-analysis found no clear differences in rate of complete clearance of scabies between products, with the exception of the rate of complete clearance after 1 week when comparing topical permethrin to oral ivermectin (relative risk 0.65, 95% confidence interval [CI] 0.54 to 0.78). However, at weeks 2 and 4, there was no difference in the rate of complete clearance for that comparison. Rates of adverse events were similar between all evaluated therapies.
- A meta-analysis evaluated 52 studies comparing treatments for scabies to each other or placebo. These treatments included sulfur, benzyl benzoate, lindane, malathion, crotamiton, permethrin, oral or topical ivermectin, synergized pyrethrins, or herbal treatments. The primary outcome was either clinical or microscopic cure. Secondary outcomes included persistent itching and adverse events. Results of the direct meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane and crotamiton at 1 to 2 weeks and 3 to 6 weeks. Oral ivermectin demonstrated better cure rates than lindane. For persistent itching, oral ivermectin was significantly better than benzyl benzoate and lindane; permethrin was significantly better than lindane. No significant differences between treatments were observed in adverse events. According to the network meta-analysis, the highest probability of cure at 3 to 6 weeks was associated with permethrin + oral ivermectin followed by permethrin alone and topical ivermectin. Topical ivermectin followed by permethrin were the highest ranked to reduce persistent itching. The agents with the lowest probability for adverse events were synthetic pyrethrins, malathion, and oral ivermectin. Sulfur ranked highest in the probability for adverse events followed by permethrin + oral ivermectin (*Thadanipon 2019*).

Lice

- Benzyl alcohol has been evaluated in 2 multicenter, randomized, double-blind, vehicle-controlled studies in patients (6 months of age and older) with an active head lice infestation (N = 628). In both studies, 2 applications of benzyl alcohol were associated with a significantly greater chance of treatment success (zero live lice 14 days following final treatment) compared to vehicle (p < 0.001). The absolute difference in treatment success rates in study I was 71.4% in favor of benzyl alcohol (95% CI, 61.8 to 85.7%) and 48.8% (95% CI, 31.1 to 62%) in study II, again in favor of benzyl alcohol. In both studies, there was a lower incidence of treatment failure associated with benzyl alcohol compared to vehicle (3.3 vs 83.6% and 14.3 vs 60.7% in studies I and II, respectively; p < 0.001 for both) (*Meinking et al 2010*).
- Permethrin has demonstrated a higher rate of treatment success compared to Lindane in the treatment of lice following a single application (*Brandenburg et al 1986, Bowerman et al 1987, Kalter et al 1987, Taplin et al 1986a*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin has been shown to be significantly more efficacious (*Carson et al 1988, DiNapoli et al 1988*). Carson et al reported a cure rate of 96.3% for permethrin and a cure rate of 45.2% for the combination of pyrethrins and piperonyl butoxide at 7 days following treatment (p < 0.005) (*Carson et al 1988*). In multiple studies, malathion has been reported to be pediculicidal and ovicidal or had higher rates of cure when compared to permethrin (*Meinking et al 2004, Meinking et al 2007, Roberts et al 2000*).
- Two identical, vehicle-controlled studies demonstrating the safety and efficacy of ivermectin lotion in the treatment of head lice were completed in 781 patients (6 months of age and older) with head lice. The 2 studies showed that a higher percentage of patients treated with ivermectin lotion, without nit combing, were treatment responders (free of live lice at day 2 and through day 8 to the final evaluation at day 15) following a single application compared to vehicle application (combined study results for day 2: 94.9 vs 31.3%, respectively; day 8: 85.2 vs 20.8%, respectively; day 15: 73.8 vs 17.6%, respectively; p < 0.001 for each comparison). (*Pariser et al 2012*).

- Spinosad has been evaluated in 2 randomized, active-controlled trials of 1038 patients aged 6 months or older with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of lice-free patients compared to permethrin with nit combing ($p < 0.001$ for both trials). Moreover, the majority of patients treated with spinosad required only 1 course of treatment, compared to the majority of permethrin-treated patients who required 2 courses of treatment (p values not reported) (*Stough et al 2009*).

CLINICAL GUIDELINES

Scabies

- Current treatment guidelines from the CDC and the AAP state that permethrin 5% cream is the drug of choice for children 2 months of age and older with scabies. Crotamiton is available as another option for adult patients, but frequent treatment failures have been reported with this agent. Oral ivermectin may be considered for patients who fail treatment or for those who cannot tolerate topical therapies. Lindane is not recommended due to the risk of neurotoxicity, and the lotion formulation that was FDA-approved for scabies has been discontinued (*AAP Red Book 2018*, *CDC 2018*, *Clinical Pharmacology 2019*, *Gunning et al 2012*, *Strong et al 2010*, *WHO 2019*).
- Crusted scabies should be treated using oral ivermectin in combination with a topical agent (*CDC 2018*).
- Household members and sexual contacts of the affected individual should be treated even if they do not have any signs of an infestation, as it can take 2 to 5 weeks for symptoms to develop. To prevent re-infestation, all patients should be treated at the same time (*CDC 2018*).
- All clothing, bedding, and towels require decontamination by laundering in hot water and drying in a hot dryer, dry-cleaning, or sealing in a plastic bag for 72 hours. The use of a fumigant or insecticide spray is not recommended (*CDC 2018*).

Lice

- The CDC and the AAP recommend permethrin 1% as first-line antiparasitic therapy for the treatment of lice. For the treatment of head lice, therapy should be initiated with permethrin 1% or pyrethrins when there is no known resistance. Malathion (in patients 6 years of age or older) and benzyl alcohol (in patients 6 months of age and older) may be used when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Per the AAP, spinosad and ivermectin might prove helpful in difficult cases, but the cost of these preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP for use in treatment of head lice (*AAP Red Book 2018*, *CDC 2015[a]*, *CDC 2015[b]*, *CDC 2016*, *Devore et al 2015*, *Downs et al 1999*, *Gunning et al 2012*).
- All clothing, bedding, and towels should be laundered in hot water and dried in a hot dryer to avoid another infestation. Items that cannot be washed can be placed in a hot dryer for 20 to 30 minutes, dry-cleaned, or sealed in a plastic bag for 2 weeks; combs and brushes should be soaked in hot water (at least 130 degrees Fahrenheit) for 5 to 10 minutes. The use of fumigants is not recommended (*CDC 2015[a]*, *CDC 2015[b]*, *CDC 2016*).
- Non-pharmacological tactics should be used to treat body lice, such as laundering clothing and bedding in hot water as well as regular bathing. If the prescriber determines that pharmacological treatment is necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2015[a]*, *Gunning et al 2012*).
- The CDC recommends permethrin 1% or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pubic lice (*CDC 2015[b]*).

SAFETY SUMMARY

- Lindane carries a boxed warning for therapy placement, neurologic toxicity, contraindications, and proper use.
 - Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications.
 - Neurologic toxicity has been reported with Lindane use, including seizures and deaths; use with caution in infants, children, the elderly, individuals with other skin conditions, and individuals who weigh less than 110 pounds (50 kg).
 - Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.
 - Patients should be instructed on the proper use of Lindane including amount to apply, how long to leave on, and avoiding retreatment.
- Lindane is contraindicated in patients with crusted (Norwegian) scabies and other skin conditions such as atopic dermatitis or psoriasis that may increase systemic absorption of the drug.

- Malathion lotion is contraindicated in neonates and infants because their scalps are more permeable and may have increased absorption of malathion. Malathion lotion is flammable; patients should be instructed to allow hair to dry naturally after application and avoid use of any electric heat source.
- All topical scabicide and pediculicide products are contraindicated in patients with a sensitivity or allergy to any active or inactive ingredient in the product.
- For the class, adverse events are mostly dermatological in nature.
- Lindane should be used with caution with any drug that is known to lower the seizure threshold. Drug interactions for the remaining products in this class are minimal due to the topical application.
- Products have not been evaluated in the elderly; caution should be exercised when used in this population.

Table 3. Specific Populations

Drug	Pregnancy	Nursing Mothers	Pediatrics
Eurax (crotamiton)	Category C*	Lactation information is not available from the manufacturer so it is unknown whether excreted in breast milk; use with caution.	Safety and effectiveness in pediatric patients have not been established.
Lindane (gamma-hexachlorocyclohexane)	Category C*	Enters breast milk; use is contraindicated. Discard milk for at least 24 hours after application.	Avoid use in infants and young children due to a higher incidence of adverse reactions and risk of toxicity in this age group.
Natroba (spinosad)	Category B*	Spinosad is not present in breast milk. However, Natroba also contains benzyl alcohol which may be systemically absorbed through the skin. Use only if benefits outweigh the risks and discard breast milk for at least 8 hours after use.	Should not be used in children younger than 6 months old due to risk of benzyl alcohol toxicity.
Ovide (malathion)	Category B*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 6 years old.
Permethrin	Category B*	Unknown whether excreted in breast milk; due to tumorigenic potential in animal studies, consider discontinuing nursing temporarily or withholding the drug while nursing	Should not be used in children younger than 2 months old.
Piperonyl butoxide and pyrethrins	Category C*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 2 years old.
Sklice (ivermectin)	Unclassified [†] : No studies evaluating use in pregnant women. Observational studies have not revealed adverse effects; but these studies cannot definitively rule out any drug-associated risk.	Following oral administration, it is excreted in human milk in low amounts; this has not been evaluated following topical administration.	Should not be used in children younger than 6 months old.

Drug	Pregnancy	Nursing Mothers	Pediatrics
Ulesfia (benzyl alcohol)	Category B*	Unknown whether excreted in breast milk, but benzyl alcohol may be absorbed through the skin; use with caution.	Should not be used in children younger than 6 months old.

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

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

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Eurax (crotamiton)	Cream (Eurax), lotion (Eurax)	Topical	Apply thoroughly from chin to toes, including skin folds and under fingernails; a second application is recommended 24 hours later. A cleansing bath should be taken 48 hours after the last application.	
Lindane (gamma-hexachlorocyclohexane)	Shampoo	Topical	Apply to dry hair and leave in place for 4 minutes. Then add a small amount of water until a good lather forms and immediately rinse. Retreatment is not recommended.	
Natroba (spinosad)	Suspension	Topical	Apply to dry scalp and hair; wash off after 10 minutes. A second treatment may be applied after 7 days if live lice are still seen.	
Ovide (malathion)	Lotion	Topical	Apply to dry hair. Leave on 8 to 12 hours then shampoo and rinse. May repeat with a second application after 7 to 9 days if lice are still present.	Product is flammable; avoid smoking, open flame, and hair dryers. Allow hair to dry naturally and uncovered.
Permethrin	Cream, crème rinse, lotion	Topical	Scabies: Apply cream from head to soles of feet. Wash off after 8 to 14 hours. Application may be repeated after 14 days if live mites are still present. Lice: Apply crème rinse/lotion on the scalp and damp hair. Leave on for 10 minutes then rinse with water. May repeat after 7 days if live lice are still present.	The 5% cream formulation is approved for scabies and is available by prescription only; the 1% crème rinse and lotion are approved for head lice and are available OTC.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Piperonyl butoxide and pyrethrins	Shampoo, crème rinse	Topical	Apply to hair and scalp. Leave on for no more than 10 minutes then rinse. Treatment should be repeated after 7 to 10 days on dry hair.	If first application is applied on wet hair, reapply after 24 hours.
Sklice (ivermectin)	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse with water. Wait 24 hours before using shampoo. For single use only; do not re-treat.	
Ulesfia (benzyl alcohol)	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse. Repeat treatment after 7 days.	

See the current prescribing information for full details

CONCLUSION

- There are a number of effective topical scabicide and pediculicide agents available including Eurax (crotamiton), Lindane (gamma-hexachlorocyclohexane), Ovide (malathion), Natroba (spinosad), permethrin (Elimite 5%, NIX 1%), piperonyl butoxide with pyrethrins (RID), Sklice (ivermectin) and Ulesfia (benzyl alcohol). Permethrin is recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States (*Downs et al 1999, CDC 2016, Devore et al 2015*).
- Topical insecticides exert their pediculicidal and scabidical effects through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuroexcitation, theoretically lowering the risk of resistance. Ivermectin and spinosad are 2 newer agents approved for the treatment of head lice. Spinosad is not extensively metabolized, and therefore, it is still present and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application (*Villegas et al 2012*). Ivermectin has been approved for one-time use. Permethrin 1% and the combination of pyrethrins and piperonyl butoxide are available OTC (*CDC 2016*). Lindane, a well-known older agent, is reserved as second-line therapy and carries a boxed warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should resistance occur, or if a patient experiences treatment failure with a first-line product (*CDC 2016, Devore et al 2015*).
- Limited direct comparisons have been completed with agents in this class. Permethrin has demonstrated a higher rate of treatment success compared to Lindane in the treatment of lice following a single application (*Brandenburg et al 1986, Bowerman et al 1987, Taplin et al 1986a*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (*Carson et al 1988, DiNapoli et al 1988*). Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with Lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*); however, one study found no difference at days 15 and 29 following treatments (*Chouela et al 1999*). In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin (*Meinking et al 2004, Roberts et al 2000*).
- The newer agents, which include benzyl alcohol, ivermectin, and spinosad, have shown cure rates (lice-free at day 14 or 15) of 75 to 76%, 71 to 76% and 84.6 to 86.7%, respectively, although there is limited published literature confirming these results.
- A comparison of the overall success rates for the topical scabicide products shows 89 to 100% success with permethrin, 65 to 92% with Lindane, and 60 to 88% with Eurax. **A meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane and crotamiton at 1 to 2 weeks and 3 to 6 weeks (*Thadanipon 2019*).** Current clinical guidelines recommend permethrin 5% as the drug of choice for the treatment of scabies. Lindane is not recommended due to its toxicity, and the lotion formulation that was approved for scabies has been discontinued; the

shampoo formulation is only approved for lice and should be reserved for patients who have exhausted medication options that pose less risk. For crusted scabies, oral ivermectin should be co-administered with a topical agent.

- Overall, topical pediculicides are effective in eradicating head lice, but generally do not have any effect on ova (nits). The guidelines from CDC and AAP recommend permethrin 1% or the combination of pyrethrins and piperonyl butoxide for head lice when resistance is not suspected (*AAP Red Book 2018, CDC 2016, Devore et al 2015*). Retreatment of head lice usually is recommended because most approved pediculicides are not completely ovicidal. Spinosad and malathion are the only ovicidal medications for the treatment of head lice, but the need for re-treatment has been reported (*CDC 2016*). Lindane is no longer recommended by the AAP for the treatment of head lice (*Devore et al 2015*).
- Body lice can be managed with nonpharmacological tactics such as laundering clothes and bedding in hot water and regular bathing. Should pharmacological treatment be necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2015[a], Gunning et al 2012*).
- The CDC recommends permethrin or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pediculosis pubis (*CDC 2015[b]*).

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Publication Date: February 25, 2019

Topical Immunomodulators





Prior Authorization Guideline

Guideline Name Topical Immunomodulators

1 . Indications

<p>Drug Name: Eucrisa (crisaborole) ointment</p> <p><u>Indications</u></p> <p>Atopic Dermatitis Indicated for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.</p>
<p>Drug Name: Elidel (pimecrolimus) cream</p> <p><u>Indications</u></p> <p>Atopic Dermatitis Second-line therapy for short-term and noncontinuous long-term treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients 2 years and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.</p>
<p>Drug Name: Protopic (tacrolimus) ointment</p> <p><u>Indications</u></p> <p>Atopic Dermatitis Treatment of moderate to severe atopic dermatitis in immunocompetent patients not responsive to conventional therapy or when conventional therapy is not appropriate</p>

2 . Criteria

Diagnosis	Atopic Dermatitis
Approval Length	12 Month

Coverage and Limitations

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

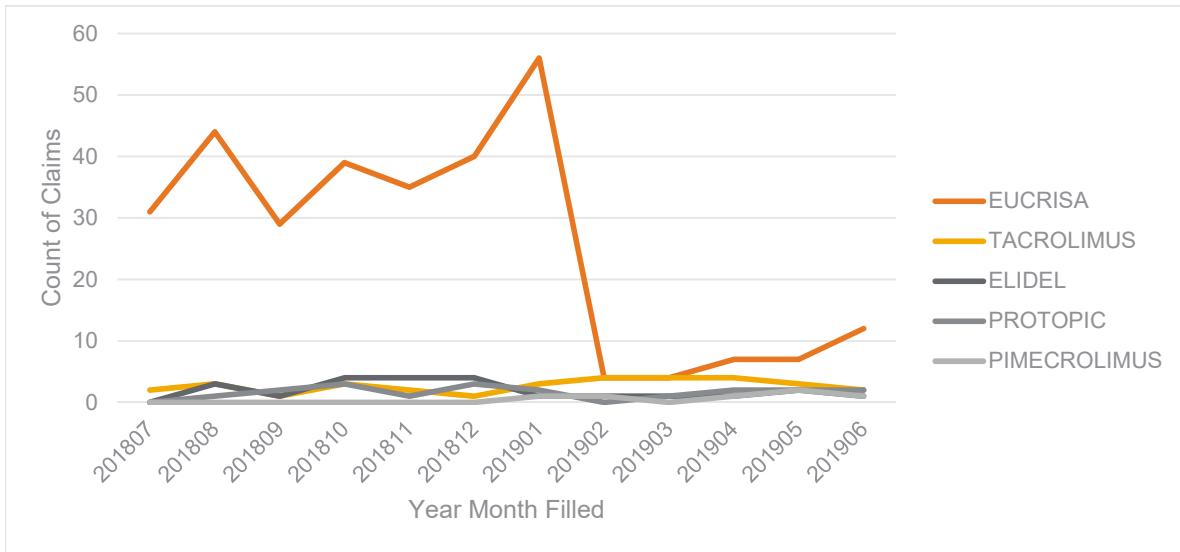
- a. Patient must have a therapeutic failure with the use of a topical steroid.
- b. Patient has a documented diagnosis of Atopic Dermatitis:
 1. Elidel® for mild to moderate, for ages > two years.
 2. Eucrisa® for mild to moderate, for ages ≥ two years.
 3. Protopic® 0.03%; moderate to severe, for ages > two years.
 4. Protopic® 0.1%; moderate to severe, for ages > 18 years.
- c. Not for chronic use.
- d. Elidel® is not recommended for use on patients with Netherton's syndrome due to the potential for systemic absorption.
- e. The recipient must have had therapeutic failure with the trial of a topical steroid of at least 14 days within the last six months for approval of Eucrisa®.
- f. Not recommended for use in immunocompromised patients.

Topical Immunomodulator Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
ELIDEL	12	23	428	860
EUCRISA	179	308	8,780	19,300
PIMECROLIMUS	3	6	149	180
PROTOPIC	6	19	485	1,130
TACROLIMUS	16	32	724	1,370



* PA Criteria on Eucrisa effective February 4, 2019

M. Topical Immunomodulators

Therapeutic Class: Topical Immunomodulators

Eucrisa® last reviewed by the DUR Board: July 26, 2018

Last Reviewed by the DUR Board: April 26, 2007

Topical Immunomodulators drugs are a subject to prior authorization and quantity limitations 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

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

- a. Patient must have a therapeutic failure with the use of a topical steroid.
 - b. Patient has a documented diagnosis of Atopic Dermatitis:
 1. Elidel® for mild to moderate, for ages \geq two years.
 2. Eucrisa® for mild to moderate, for ages \geq two years.
 3. Protopic® 0.03%; moderate to severe, for ages \geq two years.
 4. Protopic® 0.1%; moderate to severe, for ages \geq 18 years.
 - c. Not for chronic use.
 - d. Elidel® is not recommended for use on patients with Netherton's syndrome due to the potential for systemic absorption.
 - e. The recipient must have had therapeutic failure with the trial of a topical steroid of at least 14 days within the last six months for approval of Eucrisa®.
 - f. Not recommended for use in immunocompromised patients.
2. Prior Authorization forms are available at:
<http://www.medicaid.nv.gov/providers/rx/rxforms.aspx>

Therapeutic Class Overview

Anti-inflammatory Agents – Misc., Topical

INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2% to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States (*Berke et al 2012, Eichenfield et al 2014a, Food and Drug Administration [FDA] presentation 2015*). Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of 5 years (*Eichenfield et al 2014a*).
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors (*Weston & Howe 2018*). Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious “itch-scratch” cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization, and secondary infection (*Castro 2008*). The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces (*Eichenfield et al 2014a*). The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities (*Eichenfield et al 2014a*).
- Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment for atopic dermatitis, and there is no known cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin’s abnormal barrier function, hydrating the skin, and controlling active disease with topical anti-inflammatory agents (*Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014*).
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine) (*Eichenfield et al 2014b*). However, evidence supporting their use is weak due to lack of controlled trials.
- Topical corticosteroids are considered to be the standard of care for the treatment of atopic dermatitis (*Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014*). Low- to high-potency topical corticosteroids are utilized 1 or more times daily for the treatment of acute flares, as well as intermittently to prevent relapses. One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application (*Krakowski et al 2008*). There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck (*Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013*).
- Immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). The exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis (*Clinical Pharmacology 2019*). Protopic and Elidel provide immunosuppression via inhibition of T-cell activation.
- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents (*FDA press release 2006*). This updated labeling was a result of cancer-related adverse events (AEs) with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. The labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under 2 years of

age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established.

- Eucrisa (crisaborole) is a non-steroidal, topical treatment for atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis (Zane *et al* 2016). Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines (Paller *et al* 2016). The novel boron chemistry of Eucrisa additionally enables synthesis of a low molecular weight compound that facilitates effective penetration through human skin (Paller *et al* 2016).
- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical; Macrolide Immunosuppressants - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Elidel (pimecrolimus)	✓
Protopic (tacrolimus)	✓
Eucrisa (crisaborole)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.	✓		
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✓ *	
Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older			✓

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age.

(Prescribing information: Elidel 2017, Eucrisa 2017, Protopic 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

Elidel and Protopic

- The FDA approval of Elidel cream was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (N = 589). Two of these 3 trials support the use of Elidel cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-

Data as of March 4, 2019 LS/KMR

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week, vehicle-controlled, Phase III trials were conducted in pediatric patients 2 to 17 years of age (N = 403). These studies showed significant clinical response based on physician's global evaluation for Elidel-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.

- The FDA approval of Protopic ointment was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (N = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the Protopic group compared to the vehicle group ($p < 0.001$). There was some evidence that Protopic 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the Protopic strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Elidel and Protopic have been directly compared in clinical trials. One trial compared Elidel 1% to Protopic 0.03% in patients 2 to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study (*Kempers et al 2004*). However, itching was reported at a significantly higher rate in the Protopic group. In 2 other clinical trials, Protopic 0.1% was compared to Elidel in adult patients over 6 weeks. Patients treated with Protopic had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with Elidel (*Abramovits et al 2008, Fleischer et al 2007*). The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the Protopic group in both studies (*Abramovits et al 2008, Fleischer et al 2007*). There were no differences in AEs between the groups.
- A meta-analysis of 3 randomized clinical trials showed that both adults and children in the Protopic-treated group had a significantly greater improvement in EASI score at week 6 as compared to the Elidel group (*Paller et al 2005*). The most common AEs in all studies were local application site reactions including burning and stinging (*Paller et al 2005*).
- A meta-analysis of 25 randomized controlled trials (N = 6897) showed that Protopic 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis (*Ashcroft et al 2005*). Additionally, Elidel was found to be less effective than potent topical corticosteroids (*Ashcroft et al 2005*). Individual clinical trials have reported conflicting results (*Bieber et al 2007, Doss et al 2009, Doss et al 2010*).
- A meta-analysis and systematic review assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N = 7378) (*Ei-Batawy et al 2009*). In terms of overall comparison, Elidel was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 weeks) than Elidel in the treatment of moderate to severe atopic dermatitis. Although this meta-analysis showed that Elidel seems to be less effective than topical corticosteroids, Elidel would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of Protopic trials demonstrated that Protopic was more effective than vehicle (*Ei-Batawy et al 2009*). When compared to mild potency topical corticosteroids like hydrocortisone acetate, Protopic was more efficacious. However, when compared to moderate potency topical corticosteroids, Protopic 0.03% was significantly less effective than topical corticosteroids, and Protopic 0.1% was equal in effectiveness to the topical corticosteroids. Overall, Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids (*Ei-Batawy et al 2009*).
- A systematic review of 20 randomized controlled trials (N = 6288) showed that Protopic was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis (*Chen et al 2010*). Additionally, Elidel was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, 3 trials comparing Elidel to Protopic were identified. While 2 of the trials did find Protopic to be significantly more efficacious, no significant difference was found in the third trial.
- A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to Elidel or Protopic was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to Protopic and not Elidel ($p < 0.001$, $p = 0.086$, respectively) (*Hui et al 2009*).

Eucrisa

- The safety and efficacy of Eucrisa were demonstrated in 2 identically designed, randomized, Phase III, double-blind, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and $\geq 5\%$ treatable BSA (*Eucrisa formulary submission dossier 2016, Paller et al 2016*). The primary endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2 -grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8% vs 25.4%, $p = 0.038$; Study AD-302: 31.4% vs 18.0%, $p < 0.001$), with a greater percentage achieving clear/almost clear overall (51.7% vs 40.6%, $p = 0.005$; 48.5% vs 29.7%, $p < 0.001$). In addition, Eucrisa-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both $p < 0.001$).
 - An open-label extension trial of AD-301 and AD-302 evaluated the safety of Eucrisa in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with Eucrisa (93.1%). The most commonly observed AEs ($\geq 1\%$ of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).

CLINICAL GUIDELINES

- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc.) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low to high potency topical corticosteroids are the standard of care, and strength is selected based on severity, duration of treatment, location of exacerbation, and age of the patient. Elidel and Protopic are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids. Eucrisa has not yet been added to the guidelines (*Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014*).

SAFETY SUMMARY

Elidel and Protopic

- **Boxed warning:** Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
 - Avoid continuous long-term use, in any age group, and limit application to areas of involvement with atopic dermatitis.
 - Both agents are not indicated for use in children less than 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Elidel is indicated for children 2 years and older and adults.
- **Key Warnings/Precautions:**
 - Do not use on malignant or pre-malignant skin conditions.
 - Resolve bacterial or viral infections at the treatment site.
 - While using avoid exposure to sunlight.
 - Do not use in immunocompromised patients.
- **AEs:** Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.
- A 5-year, open-label, multicenter study evaluated the use of Elidel in 2418 infants compared to topical corticosteroids (*Sigurgeirsson et al 2015*). The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of 0 to 5 on the Investigator's Global Assessment (IGA). Topical corticosteroids included low potency such as hydrocortisone 1% or medium potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More Elidel patients reported bronchitis ($p = 0.02$), infected eczema ($p < 0.001$), impetigo ($p = 0.045$), and nasopharyngitis ($p = 0.04$). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the Elidel-treated group. Over the 5-year period, 88.7% and 92.3% of the Elidel- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of Elidel- and corticosteroid-treated patients completing the study.

Eucrisa

- **Contraindications:** Known hypersensitivity to Eucrisa or any component of the formulation

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- Warnings/precautions:
 - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately and appropriate therapy initiated.
- AEs:
 - In pivotal studies AD-301 and AD-302, 1012 patients (2 to 79 years of age) with mild to moderate atopic dermatitis were treated with Eucrisa twice daily for 4 weeks. The AE reported by $\geq 1\%$ of Eucrisa-treated patients (45/1012 [4%] vs. 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common ($< 1\%$) AEs in patients treated with Eucrisa included contact urticaria.
 - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study (*Eucrisa formulary submission dossier 2016, Paller et al 2016*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	<p>Do not use in children less than 2 years of age.</p> <p>Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated.</p> <p>If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis.</p> <p>Continuous long-term use should be avoided, and application should be limited to areas of involvement.</p>
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	<p>Do not use in children less than 2 years of age.</p> <p>Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated.</p> <p>If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis.</p> <p>Continuous long-term use should be avoided, and application should be limited to areas of involvement.</p>
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	<p>Safety and effectiveness in pediatric patients below the age of 2 years have not been established.</p>

See the current prescribing information for full details

CONCLUSION

- The topical calcineurin inhibitors, Elidel (pimecrolimus 1% cream) and Protopic (tacrolimus 0.03% and 0.1% ointment), are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age) who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The FDA added another agent to the atopic dermatitis armamentarium with the approval of Eucrisa (crisaborole) ointment for the topical treatment of mild to moderate atopic dermatitis in patients ≥ 2 years of age.
- The topical anti-inflammatory agents work by way of several mechanisms of action; however, the exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12). Protopic and Elidel provide immunosuppression via inhibition of T-cell activation, which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Eucrisa is a non-steroidal treatment option with a novel mechanism of action. In patients with atopic dermatitis, PDE-4 activity increases circulating inflammatory cells resulting in increased cytokine production. It is believed that Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cAMP, thereby suppressing the release of cytokines (*Clinical Pharmacology 2019, Paller et al 2016*).
- Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. A meta-analysis of 3 studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment (*Paller et al 2005*). Results favored treatment with Protopic, and AEs between the groups were similar. Another meta-analysis evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease (*Ashcroft et al 2005*). Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids (*El-Batawy et al 2009*).
- Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006 (*FDA press release 2006*). Topical calcineurin inhibitors may be associated with immunosuppression or malignancy.
- Eucrisa demonstrated short-term efficacy over vehicle ointment in 2 identically designed, 28-day, Phase III, randomized, double-blind trials; more patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Unpublished data gleaned from the 48-week, long-term study revealed no significant safety signals.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first-line treatment and recommend the use of topical Elidel or Protopic in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated or when corticosteroid-sparing measures may be desired. Eucrisa has not yet been added to the guidelines (*Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014*).

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Board Requested Reports

Opioid Utilization – top prescribers and members

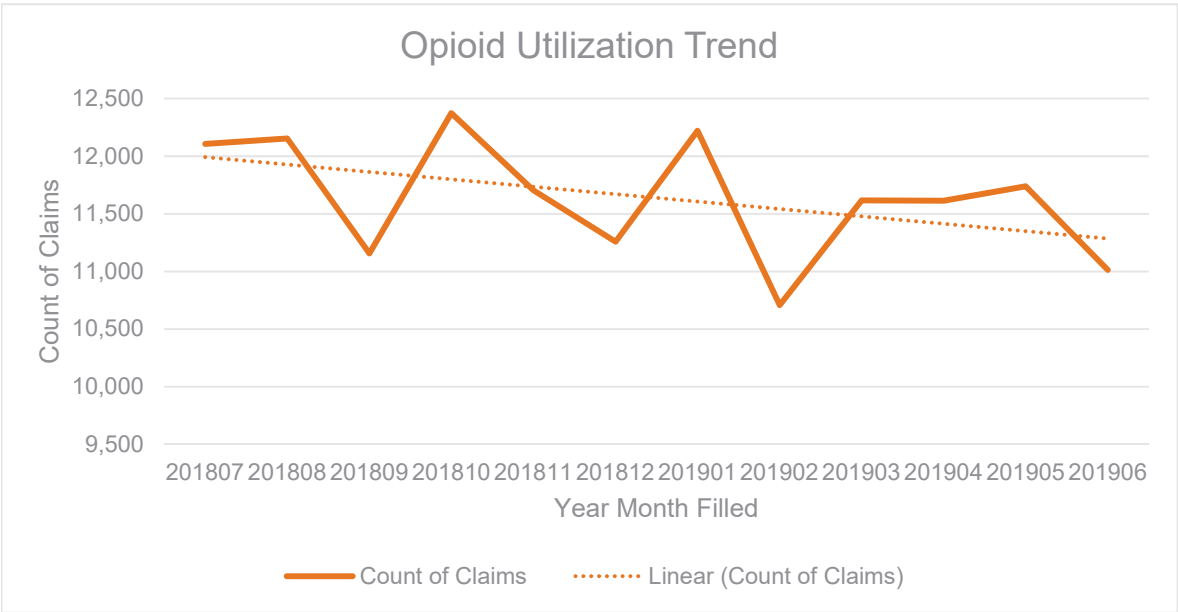


Opioid Utilization

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Date Filled	Count of Members	Count of Claims	Total Days Supply	Total Quantity
201807	8,457	12,107	221,972	756,467
201808	8,428	12,154	223,880	755,291
201809	8,027	11,157	206,032	702,653
201810	8,465	12,373	224,131	767,191
201811	8,211	11,704	216,266	740,583
201812	7,934	11,258	206,849	700,339
201901	8,542	12,220	221,446	746,798
201902	7,779	10,708	197,255	657,959
201903	8,136	11,616	209,755	695,448
201904	8,124	11,614	209,564	697,681
201905	8,027	11,738	211,670	711,730
201906	7,806	11,014	198,628	656,082



Opioid Utilization by Prescriber - Top 10

Quarter 1, 2019 and Quarter 2, 2019

Fee for Service Medicaid

Quarter 2, 2019

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Sum of MED
A	MD - Anesthesiologist	Reno	230	551	15,950	65,876	943,446
B	PA - Pain Management	Las Vegas	152	400	11,734	43,551	869,260
C	PA - No Specialty	Las Vegas	151	348	10,134	33,081	798,235
D	APRN - No Specialty	Las Vegas	271	482	13,617	45,382	588,659
E	MD - OB/GYN	Henderson	66	136	4,023	15,832	524,620
F	APRN - Neurology	Las Vegas	119	232	6,271	21,585	523,621
G	APRN - Acute Care	Las Vegas	135	285	7,462	25,790	520,550
H	APRN - Pain Management	Las Vegas	172	269	8,025	23,331	483,238
I	PA - No Specialty	Las Vegas	134	216	5,575	18,893	464,458
J	PA - No Specialty	Las Vegas	154	363	10,594	35,492	451,291

Quarter 1, 2019

Prescriber	Specialty	City	Count of Members	Count of Claims	Days Supply	Total Qty	Sum of MED
A	Anesthesiologist	Reno	255	622	17,771	74,221	1,118,633
B	PA - Pain Management	Las Vegas	160	439	12,665	47,835	966,715
C	PA - No Specialty	Las Vegas	157	366	10,848	36,467	892,673
E	MD - OB/GYN	Henderson	63	165	4,798	18,886	623,860
H	APRN - Pain Management	Las Vegas	190	315	9,368	26,534	550,268
K	PA - No Specialty	Las Vegas	147	251	7,325	27,217	533,408
L	PA - Pain Management	Las Vegas	154	270	7,864	30,148	521,164
F	APRN - Neurology	Las Vegas	136	239	6,327	21,416	507,589
J	PA - No Specialty	Las Vegas	154	366	10,627	36,159	478,374
M	MD - Pain Management	Las Vegas	139	257	6,793	22,652	470,261

Opioid Utilization by Member - Top 10

Quarter 1, 2019 and Quarter 2, 2019

Fee for Service Medicaid

Encrypted ID	Count of Claims	Sum of Days	Qty	Total MED
Mem A	10	184	1,174	60,953
Mem B	8	224	1,232	60,480
Mem C	6	180	1,080	57,600
Mem D	11	326	1,460	57,000
Mem E	11	330	790	55,800
Mem F	8	240	480	51,600
Mem G	6	180	1,320	48,900
Mem H	6	180	405	48,600
Mem I	8	240	960	48,600
Mem J	6	180	570	45,900
Mem K	6	180	720	45,900

Encrypted ID	Count of Claims	Sum of Days	Qty	Total MED
Mem A	7	194	1,605	78,525
Mem L	8	240	1,080	75,600
Mem G	8	230	1,920	69,600
Mem D	12	360	1,385	61,200
Mem C	7	172	1,080	57,600
Mem M	8	240	720	50,400
Mem N	8	240	720	50,400
Mem O	5	150	720	49,500
Mem P	8	240	960	48,600
Mem J	6	180	570	45,900
Mem K	6	180	720	45,900

Opioid Utilization by Member - Top 10 Detail

Quarter 2, 2019

Fee for Service Medicaid

Member	GPI Name	MED Value per Unit	Count of Claims	Sum of Days	Sum of Qty	Total MED
Mem A	OXYCOD TAB ER12H DETER 15MG	22.5	1	1	3	68
Mem A	OXYCODONE HCL TAB 30 MG	45	5	90	985	44,325
Mem A	OXYMORPH HCL TAB SR12HR 20MG	60	1	3	6	360
Mem A	OXYMORPH HCL TAB SR12HR 30MG	90	3	90	180	16,200
						60,953
Mem B	MORPHINE SULF TAB CR 60 MG	60	4	112	336	20,160
Mem B	OXYCODONE HCL TAB 30 MG	45	4	112	896	40,320
						60,480
Mem C	MORPHINE SULF TAB CR 100 MG	100	3	90	360	36,000
Mem C	OXYCODONE HCL TAB 20 MG	30	3	90	720	21,600
						57,600
Mem D	FENTANYL TD PAT 72H 100MCG/HR	720	2	60	30	21,600
Mem D	HYDROCODONE-APAP TAB 10-325 MG	10	3	90	240	2,400
Mem D	METHADONE HCL TAB 10 MG		3	86	860	
Mem D	MORPHINE SULF TAB CR 100 MG	100	3	90	330	33,000
						57,000
Mem E	FENTANYL TD PAT 72H 100MCG/HR	720	4	120	40	28,800
Mem E	FENTANYL TD PAT 72H 25MCG/HR	180	3	90	30	5,400
Mem E	OXYCODONE HCL TAB 20 MG	30	4	120	720	21,600
						55,800
Mem F	MORPHINE SULF TAB 15 MG	15	4	120	240	3,600
Mem F	MORPHINE SULF TAB CR 200 MG	200	4	120	240	48,000
						51,600
Mem G	HYDROCODONE-APAP TAB 10-325 MG	10	3	90	300	3,000
Mem G	OXYCODONE HCL TAB 30 MG	45	3	90	1,020	45,900
						48,900
Mem H	FENTANYL TD PAT 72H 100MCG/HR	720	3	90	45	32,400
Mem H	OXYCODONE HCL TAB 30 MG	45	3	90	360	16,200
						48,600
Mem I	OXYCOD TAB ER12H DETER 40MG	60	4	120	360	21,600
Mem I	OXYCODONE HCL TAB 30 MG	45	4	120	600	27,000
						48,600
Mem J	FENTANYL TD PAT 72H 100MCG/HR	720	3	90	30	21,600
Mem J	OXYCODONE HCL TAB 30 MG	45	3	90	540	24,300
						45,900
Mem K	OXYCOD TAB ER12H DETER 80MG	120	3	90	180	21,600
Mem K	OXYCODONE HCL TAB 30 MG	45	3	90	540	24,300
						45,900

Board Requested Reports

Top opioid prescribers and top benzodiazepine prescribers



Top Opioid and Top Benzodiazepine Prescribers

Quarter 2, 2019
Fee for Service Medicaid

Top Benzodiazepine Prescribers

Prescriber	Drug Label Name	Count of Members	Days Supply	Total Qty
BZ 1	ALPRAZOLAM TAB 1MG	44	3,522	10,647
BZ 2	ALPRAZOLAM TAB 1MG	75	4,755	10,440
BZ 3	ALPRAZOLAM TAB 2MG	74	5,580	9,720
BZ 4	ALPRAZOLAM TAB 1MG	21	1,500	4,015
BZ 5	ALPRAZOLAM TAB 1MG	16	1,237	3,741
BZ 4	ALPRAZOLAM TAB 2MG	20	1,620	3,700
BZ 7	ALPRAZOLAM TAB 1MG	15	990	3,540
BZ 8	DIAZEPAM SOL 5MG/5ML	8	561	3,327
BZ 9	DIAZEPAM SOL 5MG/5ML	2	152	3,300
BZ 10	DIAZEPAM SOL 5MG/5ML	9	467	3,265

Top Opioid and Top Benzodiazepine Prescribers

Quarter 2, 2019
Fee for Service Medicaid

Top 10 Opioid Prescribers and Benzodiazepine Claims

Opioid Prescriber	Count of Members	Count of Claims	Days Supply	Total Qty	Sum of MED	Drug Label Name	Count of Members BZ	Count of Claims BZ	Days Supply BZ	Total Qty BZ
A	230	551	15,950	65,876	943,446	ALPRAZOLAM TAB 0.5MG	1	1	1	2
E	66	136	4,023	15,832	524,620	ALPRAZOLAM TAB 0.25MG	1	1	30	90
E	66	136	4,023	15,832	524,620	ALPRAZOLAM TAB 0.5MG	1	1	30	90
E	66	136	4,023	15,832	524,620	ALPRAZOLAM TAB 1MG	5	9	270	780
E	66	136	4,023	15,832	524,620	ALPRAZOLAM TAB 2MG	15	33	990	2,760
E	66	136	4,023	15,832	524,620	DIAZEPAM TAB 10MG	1	1	30	60
E	66	136	4,023	15,832	524,620	DIAZEPAM TAB 5MG	2	3	120	240
E	66	136	4,023	15,832	524,620	LORAZEPAM TAB 1MG	1	1	30	90
E	66	136	4,023	15,832	524,620	LORAZEPAM TAB 2MG	1	3	90	360
F	119	232	6,271	21,585	523,621	ALPRAZOLAM TAB 0.25MG	2	3	21	42
F	119	232	6,271	21,585	523,621	ALPRAZOLAM TAB 0.5MG	8	14	397	958
F	119	232	6,271	21,585	523,621	ALPRAZOLAM TAB 1MG	11	17	480	1,395
F	119	232	6,271	21,585	523,621	ALPRAZOLAM TAB 2MG	3	7	210	435
F	119	232	6,271	21,585	523,621	DIAZEPAM TAB 10MG	3	5	127	249
F	119	232	6,271	21,585	523,621	DIAZEPAM TAB 2MG	2	5	82	201
F	119	232	6,271	21,585	523,621	DIAZEPAM TAB 5MG	9	11	315	630
F	119	232	6,271	21,585	523,621	LORAZEPAM TAB 1MG	1	1	7	21
F	119	232	6,271	21,585	523,621	XANAX TAB 2MG	1	2	55	100
I	134	216	5,575	18,893	464,458	ALPRAZOLAM TAB 0.25MG	3	4	65	116
I	134	216	5,575	18,893	464,458	ALPRAZOLAM TAB 0.5MG	6	7	172	291
I	134	216	5,575	18,893	464,458	ALPRAZOLAM TAB 1MG	16	22	527	1,358
I	134	216	5,575	18,893	464,458	ALPRAZOLAM TAB 2MG	7	10	254	538
I	134	216	5,575	18,893	464,458	DIAZEPAM TAB 10MG	5	11	236	506
I	134	216	5,575	18,893	464,458	DIAZEPAM TAB 2MG	1	1	7	21
I	134	216	5,575	18,893	464,458	DIAZEPAM TAB 5MG	6	6	180	360
I	134	216	5,575	18,893	464,458	LORAZEPAM TAB 0.5MG	2	2	21	70
I	134	216	5,575	18,893	464,458	LORAZEPAM TAB 1MG	2	2	44	88
I	134	216	5,575	18,893	464,458	LORAZEPAM TAB 2MG	1	2	60	120
I	134	216	5,575	18,893	464,458	XANAX TAB 2MG	1	1	30	50
H	172	269	8,025	23,331	483,238	DIAZEPAM TAB 10MG	1	1	30	20
H	172	269	8,025	23,331	483,238	DIAZEPAM TAB 2MG	1	1	5	5
H	172	269	8,025	23,331	483,238	DIAZEPAM TAB 5MG	3	6	165	180
B	152	400	11,734	43,551	869,260	ALPRAZOLAM TAB 1MG	1	1	30	90
B	152	400	11,734	43,551	869,260	DIAZEPAM TAB 10MG	4	11	308	497
B	152	400	11,734	43,551	869,260	DIAZEPAM TAB 5MG	4	10	291	583
C	151	348	10,134	33,081	798,235	None				
D	271	482	13,617	45,382	588,659	None				
G	135	285	7,462	25,790	520,550	None				
J	154	363	10,594	35,492	451,291	None				

Board Requested Reports

Lock-in Program



Lock-In Program Report

Quarter 2, 2019

Fee for Service Medicaid

Current Active recipients in Lock-in: 806

Members Added Quarter 2

April 2019	3
May 2019	2
June 2019	6

Board Requested Reports

Naloxone utilization in members receiving opioids



Naloxone and Opioid Utilization

Quarter 2, 2019

Fee for Service Medicaid

Drug Label Name	Count of Members
NALOXONE INJ 0.4MG/ML	24
NALOXONE INJ 1MG/ML	11
NALTREXONE TAB 50MG	97
NARCAN SPR	288
VIVITROL INJ 380MG	17

Members on Opioid with Nalxone Rx	303
Members with 2 fills for Narcan Spr	280
Members with 2 fills for Narcan Spr	5
Members with 3 fills for Narcan Spr	3

Count of Members with Naloxone and the Opioid Filled

Drug Name	NALOXONE INJ 0.4MG/ML	NALOXONE INJ 1MG/ML	NALTREXONE TAB 50MG	NARCAN SPR	VIVITROL INJ 380MG
ALFENTANIL INJ 1000/2ML				1	
APAP/CODEINE TAB 300-30MG		1			
APAP/CODEINE TAB 300-60MG				1	
BELBUCA MIS 150MCG				2	
BELBUCA MIS 300MCG				1	
BELBUCA MIS 450MCG				1	
BELBUCA MIS 75MCG				1	
BUPREN/NALOX MIS 8-2MG				3	
BUPREN/NALOX SUB 2-0.5MG				1	
BUPREN/NALOX SUB 8-2MG				1	
BUPRENORPHIN SUB 2MG				1	
BUT/APAP/CAF CAP CODEINE				1	
DEMEROL INJ 25MG/ML		1			
EMBEDA CAP 30-1.2MG				1	
FENTANYL DIS 100MCG/H				1	
FENTANYL DIS 12MCG/HR				1	
FENTANYL DIS 25MCG/HR				6	
FENTANYL DIS 50MCG/HR				3	
FENTANYL DIS 75MCG/HR				3	
HYDROCO/APAP SOL 7.5-325				1	
HYDROCO/APAP TAB 10-325MG	1	2		2	62
HYDROCO/APAP TAB 5-325MG	1	1		2	18
HYDROCO/APAP TAB 7.5-325					8
HYDROMORPHON INJ 1MG/ML	1	1			10
HYDROMORPHON INJ 2MG/ML	1				9
HYDROMORPHON TAB 2MG					1
HYDROMORPHON TAB 32MG ER	1				
HYDROMORPHON TAB 4MG					4
HYDROMORPHON TAB 8MG					1
HYSINGLA ER TAB 20 MG					1
HYSINGLA ER TAB 30 MG					3
HYSINGLA ER TAB 40 MG					1
MEPERIDINE INJ 25MG/ML					2
METHADONE TAB 10MG					14
METHADONE TAB 5MG		1			3
MORPHABOND TAB 15MG ER					3
MORPHABOND TAB 30MG ER					1
MORPHABOND TAB 60MG ER					1
MORPHINE SUL INJ 10MG/ML					1
MORPHINE SUL INJ 2MG/ML					2
MORPHINE SUL INJ 4MG/ML	2	2		1	16
MORPHINE SUL INJ 50MG/ML					1
MORPHINE SUL SOL 100/5ML					2
MORPHINE SUL TAB 100MG ER					2
MORPHINE SUL TAB 15MG	1	1			9
MORPHINE SUL TAB 15MG ER		1			13

Drug Name	NALOXONE INJ 0.4MG/ML	NALOXONE INJ 1MG/ML	NALTREXONE TAB 50MG	NARCAN SPR	VIVITROL INJ 380MG
MORPHINE SUL TAB 30MG	1			1	
MORPHINE SUL TAB 30MG ER	1	1		12	
MORPHINE SUL TAB 60MG ER	1			4	
OXYCOD/APAP TAB 10-325MG	1		1	55	1
OXYCOD/APAP TAB 2.5-325				1	
OXYCOD/APAP TAB 5-325MG	2		2	7	1
OXYCOD/APAP TAB 7.5-325				9	
OXYCODONE SOL 5MG/5ML				1	
OXYCODONE TAB 10MG		3		36	
OXYCODONE TAB 15MG				35	
OXYCODONE TAB 20MG				5	
OXYCODONE TAB 20MG ER				2	
OXYCODONE TAB 30MG	1			26	
OXYCODONE TAB 30MG ER				1	
OXYCODONE TAB 40MG ER				1	
OXYCODONE TAB 5MG			1	15	
OXYCODONE TAB 80MG ER				1	
OXYCODONE TAB HCL 30MG				1	
OXYCONTIN TAB 10MG CR				2	
OXYCONTIN TAB 20MG CR				3	
OXYCONTIN TAB 30MG CR				1	
OXYCONTIN TAB 40MG CR				1	
PERCOCET TAB 10-325MG				1	
PERCOCET TAB 7.5-325				1	
PRIMLEV TAB 10-300MG				1	
SUBLOCADE INJ 300/1.5	1				
SUBOXONE MIS 12-3MG				1	1
SUBOXONE MIS 4-1MG					2
SUBOXONE MIS 8-2MG				4	13
TRAMADL/APAP TAB 37.5-325		1			
TRAMADOL HCL TAB 50MG				2	18
XTAMPZA ER CAP 13.5MG					1
ZOHYDRO ER CAP 15MG					1
ZUBSOLV SUB 1.4-0.36				1	
ZUBSOLV SUB 8.6-2.1					1

Board Requested Reports

Aranesp (darbepoetin alfa) utilization



Aranesp (darbepoetin) Utilization

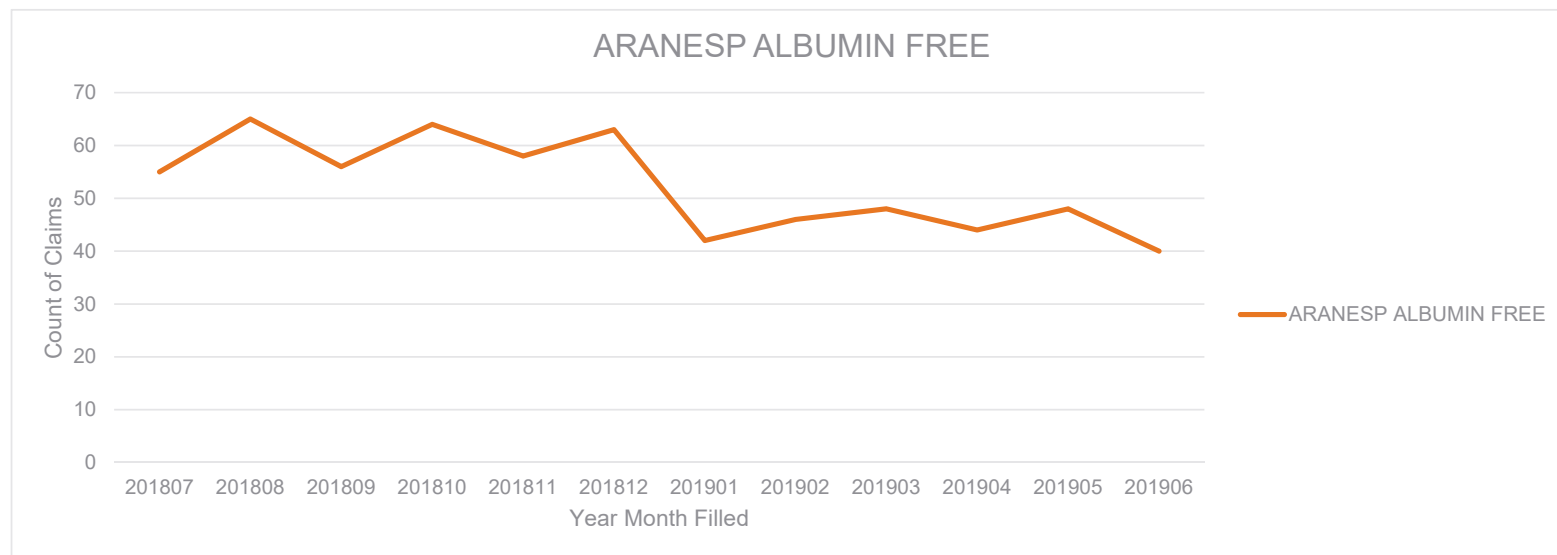
Quarter 2, 2019

Fee for Service Medicaid

Service Location	Count of Members	Count of Claims	Days Supply	Total Qty
Pharmacy Claim	6	6	238	5.6
Physician Claim	520	623	623	430.82
Total	526	629	861	436.42

Top 5 Diagnosis Codes

Diagnosis Description	Count of Members	Count of Claims	Days Supply	Total Qty
ANEMIA IN CHRONIC KIDNEY DISEASE	202	243	243	159.1
ANEMIA DUE TO ANTINEOPLASTIC CHEMOTHERAPY	109	123	123	94.2
OTHER MYELODYSPLASTIC SYNDROMES	36	47	47	31.2
ENCOUNTER FOR ANTINEOPLASTIC IMMUNOTHERAPY	30	36	36	25.6
REFRACTORY ANEMIA WITHOUT RING SIDEROBLASTS	14	15	15	13



Board Requested Reports

Antibiotic (third generation cephalosporins, fluoroquinolones and oxazolidinones) utilization



Antibiotic Utilization

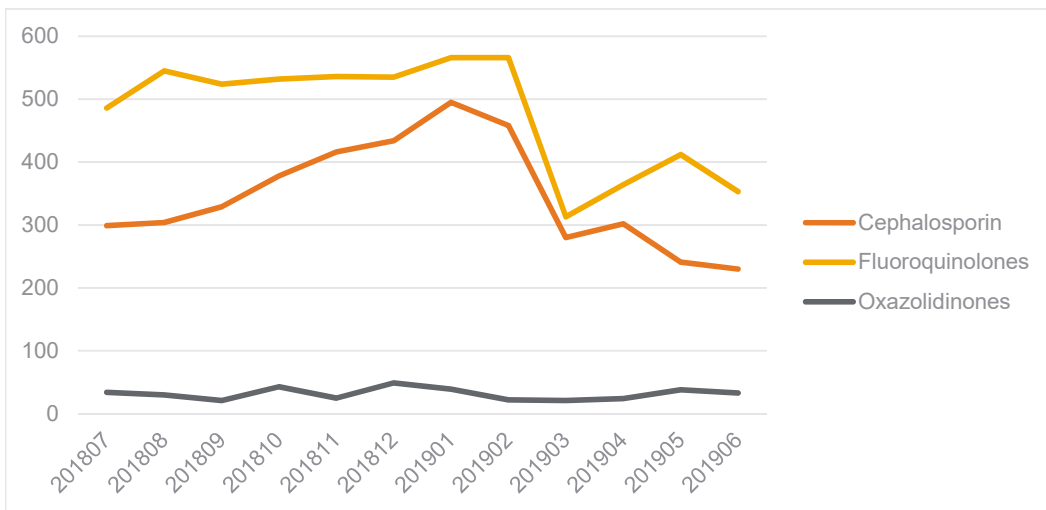
Third Generation Cephalosporins, Fluoroquinolones and Oxazolidinones

July 1, 2018 - June 30, 2019

Fee for Service Medicaid

Count of Claims

Year Month	Cephalosporin	Fluoroquinolones	Oxazolidinones	Grand Total
201807	299	486	34	819
201808	304	545	30	879
201809	329	524	21	874
201810	378	532	43	953
201811	416	536	25	977
201812	434	535	49	1018
201901	495	566	39	1100
201902	458	566	22	1046
201903	280	313	21	614
201904	302	364	24	690
201905	241	412	38	691
201906	230	353	33	616
Grand Total	4166	5732	379	10277



* PA Criteria effective March 4, 2019

Standard DUR Reports



Nevada Medicaid
Top 10 Therapeutic Classes
Fee for Service
Quarter 1, 2019 and Quarter 2, 2019

Top 10 Drug Classes by Paid Amount - Current Quarter

Drug Class Name	Count of Claims	Pharmacy Paid
ANTIHEMOPHILIC PRODUCTS**	120	\$ 13,815,305.37
ANTIRETROVIRALS**	1,770	\$ 3,623,775.23
INSULIN**	4,510	\$ 3,219,771.33
ANTICONVULSANTS - MISC.**	26,197	\$ 3,135,222.94
SYMPATHOMIMETICS**	18,610	\$ 2,812,203.98
BENZISOXAZOLES**	5,690	\$ 2,368,411.39
ANTIPSYCHOTICS - MISC.**	2,681	\$ 1,989,231.35
QUINOLINONE DERIVATIVES**	4,671	\$ 1,724,737.96
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
ANTICONVULSANTS - MISC.**	26,197	\$ 3,135,222.94
SYMPATHOMIMETICS**	18,610	\$ 2,812,203.98
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,781	\$ 208,664.17
OPIOID COMBINATIONS**	15,463	\$ 454,780.03
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,194	\$ 297,984.37
CENTRAL MUSCLE RELAXANTS**	12,282	\$ 221,737.02
HMG COA REDUCTASE INHIBITORS**	10,596	\$ 329,365.46
OPIOID AGONISTS**	10,223	\$ 638,496.19
DIBENZAPINES**	9,484	\$ 354,194.39
BENZODIAZEPINES**	8,511	\$ 107,358.70

Top 10 Drug Classes by Paid Amount - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid
ANTIHEMOPHILIC PRODUCTS**	111	\$ 12,786,149.67
ANTIRETROVIRALS**	1,797	\$ 3,364,043.23
INSULIN**	4,486	\$ 3,229,778.37
SYMPATHOMIMETICS**	20,351	\$ 3,056,475.62
ANTICONVULSANTS - MISC.**	25,703	\$ 2,960,774.38
LOCAL ANESTHETICS - TOPICAL**	1,911	\$ 2,566,389.95
HEPATITIS AGENTS**	143	\$ 2,242,904.11
BENZISOXAZOLES**	5,559	\$ 2,212,312.52
ANTIPSYCHOTICS - MISC.**	2,509	\$ 1,820,336.54
QUINOLINONE DERIVATIVES**	4,543	\$ 1,570,464.99

Top 10 Drug Classes by Claim Count - Previous Quarter

Drug Class Name	Count of Claims	Pharmacy Paid
ANTICONVULSANTS - MISC.**	25,703	\$ 2,960,774.38
SYMPATHOMIMETICS**	20,351	\$ 3,056,475.62
OPIOID COMBINATIONS**	15,654	\$ 454,888.97
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	15,640	\$ 214,609.71
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	14,248	\$ 326,832.32
CENTRAL MUSCLE RELAXANTS**	12,054	\$ 217,012.15
OPIOID AGONISTS**	10,453	\$ 647,969.95
HMG COA REDUCTASE INHIBITORS**	10,290	\$ 310,235.49
DIBENZAPINES**	9,567	\$ 386,636.91
BENZODIAZEPINES**	8,617	\$ 109,298.12

Nevada Medicaid
Concurrent Drug Utilization (ProDUR)
Fee For Service
From 4/1/19 Through 6/30/19

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
Paid	271,764	73.92%	310,806	61.45%	582,570	66.70%	\$50,170,452.52
Rejected	62,885	17.10%	158,494	31.34%	221,379	25.35%	
Reversed	32,997	8.98%	36,457	7.21%	69,454	7.95%	
Totals	367,646	100.00%	505,757	100.00%	873,403	100.00%	

cDUR Information Summary Table:

cDUR Type	Total cDURs		
	cDUR Triggered E	Count	% of All cDURs
Drug-Drug Interaction (DDI-DTMS)	502,330	158,504	43.11%
Drug Regimen Compliance (COMPLIAN)	34,693	31,742	8.63%
Dosing/Duration (DOSECHEK)	74,791	50,554	13.75%
Drug Age Caution (DRUG_AGE)	21	20	0.01%
Drug Sex Caution (DRUG_SEX)	2	2	0.00%
Duplicate Therapy (DUP THER)	145,373	60,856	16.55%
Duplicate Rx (DUPRX)	68,632	65,968	17.94%
Total All cDURs	825,842	367,646	100.00%

cDUR Type	cDURs on Paid Rxs		
	Count	% of cDUR Type	% Total cDURs
Drug-Drug Interaction (DDI-DTMS)	138,237	87.21%	50.87%
Drug Regimen Compliance (COMPLIAN)	27,766	87.47%	10.22%
Dosing/Duration (DOSECHEK)	45,387	89.78%	16.70%
Drug Age Caution (DRUG_AGE)	15	75.00%	0.01%
Drug Sex Caution (DRUG_SEX)	2	100.00%	0.00%
Duplicate Therapy (DUP THER)	42,242	69.41%	15.54%
Duplicate Rx (DUPRX)	18,115	27.46%	6.67%
Total All cDURs	271,764	73.92%	100.00%

cDUR Type	cDURs on Rejected Rxs		
	Count	% of cDUR Type	% Total cDURs
Drug-Drug Interaction (DDI-DTMS)	6,258	3.95%	9.95%
Drug Regimen Compliance (COMPLIAN)	0	0.0%	0.0%
Dosing/Duration (DOSECHEK)	331	0.65%	0.53%
Drug Age Caution (DRUG_AGE)	0	0.0%	0.0%
Drug Sex Caution (DRUG_SEX)	0	0.0%	0.0%
Duplicate Therapy (DUP THER)	13,351	21.94%	21.23%
Duplicate Rx (DUPRX)	42,945	65.10%	68.29%
Total All cDURs	62,885	17.10%	100.00%

cDUR Type	cDURs on Reversed Rxs		
	Count	% of cDUR Type	% Total cDURs
Drug-Drug Interaction (DDI-DTMS)	14,009	8.84%	42.46%
Drug Regimen Compliance (COMPLIAN)	3,976	12.53%	12.05%
Dosing/Duration (DOSECHEK)	4,836	9.57%	14.66%
Drug Age Caution (DRUG_AGE)	5	25.00%	0.02%
Drug Sex Caution (DRUG_SEX)	0	0.0%	0.0%
Duplicate Therapy (DUP THER)	5,263	8.65%	15.95%
Duplicate Rx (DUPRX)	4,908	7.44%	14.87%
Total All cDURs	32,997	8.98%	100.00%

- * 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

Nevada Medicaid
Concurrent Drug Utilization (ProDUR)
Fee For Service
From 4/1/19 Through 6/30/19

DUR Service	Top Drug Drug Interaction	Therapy / Reason	Description	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per RX	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs
Dosing/Duration (DOSECHECK)	CYCLOBENZAPRINE HYDROCHLORIDE	MAX DAYS THERAPY = 21	CENTRAL MUSCLE RELAXANTS**	Message	2,165	\$25,957.79	\$9.20	32.2	67.2	0	180
Dosing/Duration (DOSECHECK)	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	5-HT3 RECEPTOR ANTAGONISTS**	Message	989	\$422.92	\$0.36	1.7	1.5	0	21
Dosing/Duration (DOSECHECK)	IPRATROPIUM BROMIDE/ALBUTEROL SULFATE	MIN. DAYS THERAPY = 30	SYMPATHOMIMETICS**	Message	720	\$13,923.97	\$14.54	8.9	126.2	0	47
Dosing/Duration (DOSECHECK)	HEPARIN SODIUM	GERIATRIC MIN DLY = 4.00UN	HEPARINS AND HEPARINOID-LIKE AGENTS**	Message	650	\$2,054.33	\$2.09	1.0	1.6	0	20
Dosing/Duration (DOSECHECK)	IPRATROPIUM BROMIDE/ALBUTEROL SULFATE	GERIATRIC MIN DLY = 9.00UN	SYMPATHOMIMETICS**	Message	621	\$569.12	\$0.74	2.4	10.2	0	13
Dosing/Duration (DOSECHECK)	FAMOTIDINE	GERIATRIC MIN DLY = 4.00UN	H-2 ANTAGONISTS**	Message	616	\$572.15	\$0.80	1.0	2.0	0	16
Dosing/Duration (DOSECHECK)	CETIRIZINE HYDROCHLORIDE	GERIATRIC MAX DLY = .50UN	ANTIHISTAMINES - NON-SEDATING**	Message	602	\$6,870.70	\$10.58	37.3	37.3	0	32
Dosing/Duration (DOSECHECK)	LISINAPRIL	MIN. DAYS THERAPY = 7	ACE INHIBITORS**	Message	497	\$171.61	\$0.27	1.1	1.7	0	30
Dosing/Duration (DOSECHECK)	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	HMG COA REDUCTASE INHIBITORS**	Message	485	\$114.41	\$0.16	1.0	1.2	0	32
Dosing/Duration (DOSECHECK)	POTASSIUM CHLORIDE ER	ADULT MIN DLY = 2.00 UN	POTASSIUM**	Message	442	\$9,377.11	\$16.84	44.0	43.4	0	63
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/DEXTROMETHORPHAN	AGE LESS THAN 4	COUGH/COLD/ALLERGY COMBINATIONS**	Message	5	\$53.12	\$8.38	8.0	74.2	0	1
Drug Age Caution (DRUG_AGE)	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	ANTIHISTAMINES - PHENOTHIAZINES**	Message	4	\$46.11	\$8.46	5.8	115.8	0	1
Drug Age Caution (DRUG_AGE)	NITROFURANTOIN	AGE LESS THAN 4	URINARY ANTI-INFECTIVES**	Message	3	\$2,082.20	\$520.55	10.0	240.0	0	1
Drug Age Caution (DRUG_AGE)	PROMETHAZINE HCL	AGE LESS THAN 4	ANTIHISTAMINES - PHENOTHIAZINES**	Message	1	\$100.36	\$10.69	3.0	30.0	0	2
Drug Age Caution (DRUG_AGE)	ACETAMINOPHEN/CODEINE	AGE LESS THAN 10	OPIOID COMBINATIONS**	Message	1	\$17.14	\$8.57	5.0	100.0	0	0
Drug Age Caution (DRUG_AGE)	PROMETHAZINE/CODEINE	AGE LESS THAN 10	COUGH/COLD/ALLERGY COMBINATIONS**	Message	1	\$10.82	\$10.82	5.0	120.0	0	0
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	8 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	54	\$772.74	\$12.46	29.9	95.8	0	3
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	7 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	51	\$955.66	\$16.42	29.3	107.6	0	7
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	7 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	47	\$6,074.70	\$93.21	24.7	7.6	0	8
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	6 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	44	\$4,109.58	\$79.61	22.1	6.7	0	6
Drug Regimen Compliance (COMPLIAN)	GABAPENTIN	9 DAYS LATE REFILLING	ANTICONVULSANTS - MISC.**	Message	44	\$676.92	\$12.82	29.0	86.6	0	4
Drug Regimen Compliance (COMPLIAN)	ATORVASTATIN CALCIUM	8 DAYS LATE REFILLING	HMG COA REDUCTASE INHIBITORS**	Message	42	\$433.01	\$9.98	29.5	29.5	0	5
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	8 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	41	\$4,727.78	\$90.43	23.9	7.0	0	10
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	12 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	41	\$4,340.75	\$88.95	21.2	7.0	0	7
Drug Regimen Compliance (COMPLIAN)	ATORVASTATIN CALCIUM	7 DAYS LATE REFILLING	HMG COA REDUCTASE INHIBITORS**	Message	40	\$485.10	\$10.11	29.6	29.6	0	8
Drug Regimen Compliance (COMPLIAN)	PROVENTIL HFA	9 DAYS LATE REFILLING	SYMPATHOMIMETICS**	Message	37	\$4,314.70	\$90.84	21.9	7.2	0	11
Drug Sex Caution (DRUG_SEX)	BICALUTAMIDE	GENERAL CONTRAINDICATION	ANTINEOPLASTIC - HORMONAL AND RELATED AGENTS**	Message	2	\$2.50	\$1.25	30.0	30.0	0	0
Drug-Drug Interaction (DDI-DTMS)	ATORVASTATIN CALCIUM	CLOPIDOGREL TAB 75MG	HMG COA REDUCTASE INHIBITORS**	Message	869	\$12,035.20	\$9.78	49.9	50.6	0	99
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	HYDROCO/APAP TAB 10-325MG	BENZODIAZEPINES**	Message	647	\$7,965.22	\$9.62	27.6	58.3	0	29
Drug-Drug Interaction (DDI-DTMS)	AMLODIPINE BESYLATE	CLOPIDOGREL TAB 75MG	CALCIUM CHANNEL BLOCKERS**	Message	375	\$2,668.90	\$5.48	56.8	59.0	0	38
Drug-Drug Interaction (DDI-DTMS)	METFORMIN HYDROCHLORIDE	LISINAPRIL TAB 20MG	BIGUANIDES**	Message	374	\$3,885.35	\$7.61	64.8	131.9	0	38
Drug-Drug Interaction (DDI-DTMS)	ALPRAZOLAM	OXYCOD/APAP TAB 10-325MG	BENZODIAZEPINES**	Message	368	\$4,806.92	\$9.89	28.1	63.6	0	18
Drug-Drug Interaction (DDI-DTMS)	HYDROCODONE/ACETAMINOPHEN	ALPRAZOLAM TAB 1MG	OPIOID COMBINATIONS**	Message	366	\$7,647.21	\$16.15	25.8	88.0	0	19
Drug-Drug Interaction (DDI-DTMS)	TRAZODONE HYDROCHLORIDE	SERTRALINE TAB 100MG	SEROTONIN MODULATORS**	Message	354	\$4,977.25	\$9.87	32.4	43.3	0	24
Drug-Drug Interaction (DDI-DTMS)	ONDANSETRON HYDROCHLORIDE	HYDROCO/APAP TAB 5-325MG	5-HT3 RECEPTOR ANTAGONISTS**	Message	335	\$911.90	\$2.18	1.4	4.1	0	8
Drug-Drug Interaction (DDI-DTMS)	ONDANSETRON HYDROCHLORIDE	HYDROCO/APAP TAB 10-325MG	5-HT3 RECEPTOR ANTAGONISTS**	Message	328	\$2,407.42	\$5.08	3.5	9.6	0	12
Drug-Drug Interaction (DDI-DTMS)	METFORMIN HYDROCHLORIDE	LISINAPRIL TAB 10MG	BIGUANIDES**	Message	321	\$3,838.34	\$7.86	66.0	131.4	0	34
Duplicate Rx (DUPRX)	HYDROCODONE/ACETAMINOPHEN	HYDROCO/APAP TAB 10-325MG	OPIOID COMBINATIONS**	Hard Reject	4	\$5,608.02	\$22.66	26.3	108.8	276	3
Duplicate Rx (DUPRX)	ATORVASTATIN CALCIUM	ATORVASTATIN TAB 40MG	HMG COA REDUCTASE INHIBITORS**	Soft Reject	2	\$3,424.28	\$12.05	18.5	18.5	326	0
Duplicate Rx (DUPRX)	AMLODIPINE BESYLATE	AMLODIPINE TAB 10MG	CALCIUM CHANNEL BLOCKERS**	Soft Reject	1	\$2,456.49	\$10.78	30.0	30.0	297	0
Duplicate Rx (DUPRX)	EPOGEN	EPOGEN INJ 10000/ML	HEMATOPOIETIC GROWTH FACTORS**	Soft Reject	0	\$43,143.37				1,089	0
Duplicate Rx (DUPRX)	SODIUM CHLORIDE	SOD CHLORIDE INJ 0.9%	SODIUM**	Soft Reject	0	\$2,190.79				981	0
Duplicate Rx (DUPRX)	PROVENTIL HFA	PROVENTIL AER HFA	SYMPATHOMIMETICS**	Soft Reject	0	\$43,423.66				416	0
Duplicate Rx (DUPRX)	GABAPENTIN	GABAPENTIN CAP 300MG	ANTICONVULSANTS - MISC.**	Soft Reject	0	\$5,202.11				364	0
Duplicate Rx (DUPRX)	ONDANSETRON HYDROCHLORIDE	ONDANSETRON INJ 4MG/2ML	5-HT3 RECEPTOR ANTAGONISTS**	Soft Reject	0	\$165.20				322	0
Duplicate Rx (DUPRX)	HECTOROL	HECTOROL INJ 4MCG/2ML	METABOLIC MODIFIERS**	Soft Reject	0	\$1,303.50				300	0
Duplicate Rx (DUPRX)	ATORVASTATIN CALCIUM	ATORVASTATIN TAB 20MG	HMG COA REDUCTASE INHIBITORS**	Soft Reject	0	\$3,091.23				256	0
Duplicate Therapy (DUPHTER)	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	OPIOID AGONISTS**	Message	845	\$3,954.75	\$3.29	1.0	1.8	0	20
Duplicate Therapy (DUPHTER)	KETOROLAC TROMETHAMINE	NON-STEROIDAL ANTI-INFLAMMATOR	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	Message	664	\$2,668.28	\$3.36	1.0	2.4	0	3
Duplicate Therapy (DUPHTER)	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	DIBENZAPINES**	Extract	564	\$13,392.29	\$12.90	31.2	40.9	0	49
Duplicate Therapy (DUPHTER)	RISPERIDONE	ORAL ANTIPSYCHOTICS	BENZISOXAZOLES**	Extract	356	\$7,581.45	\$11.04	30.1	47.1	0	32
Duplicate Therapy (DUPHTER)	GABAPENTIN	GABAPENTIN AND RELATED	ANTICONVULSANTS - MISC.**	Extract	335	\$10,373.23	\$15.55	37.8	118.3	0	54
Duplicate Therapy (DUPHTER)	HYDROCODONE/ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	OPIOID COMBINATIONS**	Message	292	\$67.97	\$0.14	1.0	1.4	0	10
Duplicate Therapy (DUPHTER)	DEXAMETHASONE SODIUM PHOSPHATE	GLUCOCORTICOSTEROIDS	GLUCOCORTICOSTEROIDS**	Message	285	\$2,055.90	\$4.34	1.0	4.4	0	6
Duplicate Therapy (DUPHTER)	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	DIBENZAPINES**	Extract	233	\$5,767.99	\$13.80	29.9	43.8	0	19
Duplicate Therapy (DUPHTER)	ARIPIPRAZOLE	ORAL ANTIPSYCHOTICS	QUINOLINONE DERIVATIVES**	Extract	229	\$9,875.44	\$21.78	30.4	32.8	0	23
Duplicate Therapy (DUPHTER)	LEVOTHYROXINE SODIUM	THYROID HORMONES	THYROID HORMONES**	Extract	204	\$5,671.16	\$15.30	56.1	54.3	0	59
Duplicate Therapy (DUPHTER)	GABAPENTIN	GABAPENTIN AND RELATED	ANTICONVULSANTS - MISC.**	Soft Reject	0	\$17,653.88				254	0
		Total			16,596	\$328,452.00	\$1,359.65	1,108.7	2,531.204	4,881	1,125

*Ratings are based on the following order:
Total Due (Paid + Deducted + Reversed)

Nevada Medicaid

Retro-DUR Activities

Fee for Service

Quarter 2, 2019

Month	Clinical Initiative	Letters Sent	Responses	Prescribers	Recipients
April 2019	Diabetic w/o Statin	102	10	77	100
May 2019	Zolpidem Utilization	66	4	59	65
May 2019	65 and older - Benzodiazepine-Hypnotic	48	10	41	34
June 2019	Opioid Use Disorder (without CA or HIV meds)	86	7	65	86