Nevada Medicaid Drug Use Review Board Meeting

January 28, 2021

OPTUMRx®

Table of Contents

Agenda	3
DUR Summary	8
DUR Board Meeting Minutes for October 22, 2020	11
Anticonvulsants, Misc.	30
Spinal Muscular Atrophy Agents (SMA)	64
Duchenne Muscular Dystrophy (DMD)	86
Topical Neuropathic Pain Agents	106
Board Requested Reports	123
Standard Reports	128

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	December 4, 2020
Date of Meeting:	Thursday, January 28, 2021 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).
Webinar Registration:	Microsoft Teams Or https://teams.microsoft.com/l/meetup-join/19%3ameeting_ZGMxMDQ2ZDAtZjQ1Ni00MDQzLTlmNjUtOGRmMjc2MDgyMjI4%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%2242971ee7-a94c-4957-b200-48069e3c9add%22%7d Out of deference to Declaration of Emergency Directive 006) from the State of Nevada Executive Department signed by Governor Sisolak on March 22, 2020 & Emergency Directive 003 signed March 20, 2020, a physical location will not be open to the public for attendance at this time. Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email Tanya Benitez at tbenitez@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.*
Meeting Audio Information:	Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. **For Audio Only:** Phone: (952) 222-7450 Event: 216 356 890#

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

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

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

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

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from October 22, 2020.
b. Status Update by DHCFP.

4. Clinical Presentations

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

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

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for agents used in the treatment of Spinal Muscular Atrophy (SMA).

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

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for agents used in the treatment of Duchenne Muscular Dystrophy (DMD).

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

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for topical neuropathic pain agents.

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

5. DUR Board Requested Reports

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

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

6. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q2 2020 and Q3 2020 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q3 2020.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

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

7. Closing Discussion

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

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

c. Adjournment.

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

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

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

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the DHCFP as soon as possible and at least ten days in advance of the meeting, by e-mail at tbenitez@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

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

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

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

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

Summary of the DUR Board

Drug Use Review Board

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

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

The DUR Board meets quarterly to monitor drugs for:

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

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

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

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

Current Board Members:

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

Drug Use Review (DUR) Board Meeting Schedule for 2021

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

Web References

Medicaid Services Manual (MSM) Chapter 1200:

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

Drug Use Review Board Bylaws:

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

Drug Use Review Board Meeting Material:

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

Social Security Act, 1927:

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

Meeting Minutes

DRUG USE REVIEW BOARD

DRAFT MEETING MINUTES

Date of Meeting: Thursday, October 22, 2020, at 1:00 p.m.

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.

Agenda Item	Record	Notes
1. Call to Order and Roll Call	Chairwoman Wheeler called the meeting to order at 1:07 p.m. on October 22, 2020. The roll was taken by Chairwoman Wheeler. Wheeler, Jennifer, Pharm.D. – Chair: Present ☒ Absent ☐ Adeolokun, Netochi, Pharm.D. – Vice Chair: Present ☒ Absent ☐ Canty, Mark, MD: Present ☒ Absent ☐ Castaneda, Crystal, MD: Present ☐ Absent ☒ Cate, Jessica, Pharm.D.: Present ☐ Absent ☒ England, Dave, Pharm.D.: Present ☒ Absent ☐ Khan, Mohammad, MD: Present ☐ Absent ☒ Le, Brian, DO: Present ☐ Absent ☒ Owens, Michael, MD: Present ☒ Absent ☐	**DHCFP Staff Present were as follows:** Young, DuAne, Deputy Administrator Slamowitz, Beth, Pharm.D., Senior Policy Advisor Long, Holly, Social Services Program Specialist III Gudino, Antonio, Social Services Program Specialist II Woodrum, Homa, Senior Deputy Attorney General **DXC Staff Present were as follows:** Leid, Jovanna, Pharm.D.

Agenda Item	Record	Notes
	Tran, Jim, Pharm.D. ☒ ☐ A quorum was present.	**OptumRx Staff Present were as follows:** Jeffery, Carl, Pharm.D. Hansen, Sean Medina, Daniel **Managed Care Organizations representatives present were as follows:** Ryan Bitton, Health Plan of Nevada Tom Beranek, SilverSummit Health Plan Luke Lim, Anthem Blue Cross **The public attendee list included as attachment A. Note:** Participants may not have chosen to reveal their identity and in the absence of a sign-in sheet the attendee list's accuracy is not assured.
2. General Public Comment	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
3. Administrative		
a. For Possible Action: Review and Approve	No corrections were offered. Board Member England moved to approve the minutes as presented.	

Agenda Item	Record	Notes
Meeting Minutes from July 23, 2020.	Board Member Canty seconded the motion. A vote was taken, and the results were as follows from members in attendance (in favor, against, and abstentions where applicable): Wheeler, Jennifer, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adeolokun, Netochi, Pharm.D. – Vice Chair: Yes ☒ No ☐ Abst. ☐ Canty, Mark, MD: Yes ☒ No ☐ Abst. ☐ England, Dave, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Owens, Michael, MD: Yes ☒ No ☐ Abst. ☐ Tran, Jim, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
b. Status Update by DHCFP	Deputy Young updated the Board regarding Assembly Bill Three, which created a specialty pharmacy agreement. Deputy Young explained the creation of the Specialty Pharmacy Program requires a 1915B Waiver with the Centers for Medicare and Medicaid Services or CMS that allows the State Medicaid program to restrict the recipient's choice for such things as specialty pharmacy. Deputy Young detailed the opportunity for public comment on the State Plan Amendment that will go to a public hearing after the contract has been signed and CMS has agreed to the Waiver. Deputy Young continued describing the provider rate cuts of 6% and referred the board to the DHCFP website for more information. Deputy Young detailed the increase in the Medicaid population to 749,000 members resulting in budget concerns. Deputy Young paused for questions before announcing the retirement of Pharmacy Chief, Tammy Moffitt, and the resignation of Social Services Program Specialist III, Holly Long who is leaving the State. There were no questions.	Deputy Young directed the Board to the DCHFP website (https://dhcfp.nv.gov) for more information about frequently asked questions on updated provider rates.
4. Clinical Presentations		
a. For Possible Action: Discussion and possible adoption of updated		

Agenda Item	Record	Notes
prior authorization criteria and/or quantity limits for topical antipruritics.		
i. Public Comment on proposed clinical prior authorization data.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii. Presentation of utilization and clinical information	Dr. Jeffery highlighted doxepin cream's increasing utilization and approved indication for the use of short-term management of moderate pruritis in adults. Dr. Jeffery discussed a study from 2000 that found doxepin at 3.3% is shown to benefit patients with neuropathic pain compared to placebo, but this is a compounded strength and is not commercially available. Dr. Jeffery described the reason for adding prior authorization because it is being used off-label for greater than eight days and is not shown to be effective. Dr. Jeffery described the proposed criteria as requiring a diagnosis of atopic dermatitis, the patient is over 18 years of age, and the treatment duration does not exceed eight days. Dr. Lim agreed with the presented criteria. Dr. Bitton agreed with the presented criteria. Mr. Beranek agreed with the presented criteria.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler suggested adding a max quantity of one 45-gram tube every 30 days. Board Member Owens asked the presenter if the eight-day limit is per month. Dr. Jeffery responded the literature does not specify. Dr. England agreed with adding a limit of one 45-gram tube every 30 days.	

Agenda Item	Record	Notes
iv. Proposed adoption of updated prior authorization criteria	Board Member Owens moved to approve and adopt the criteria as presented with the addition of a limit of one 45-gram tube every 30 days, and Board Member Adeolokun seconded. A vote was held: Wheeler, Jennifer, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adeolokun, Netochi, Pharm.D. – Vice Chair: Yes ☒ No ☐ Abst. ☐ Canty, Mark, MD: Yes ☒ No ☐ Abst. ☐ England, Dave, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Owens, Michael, MD: Yes ☒ No ☐ Abst. ☐ Tran, Jim, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
b. For Possible Action: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for multiple sclerosis (MS) agents.		
i. Public Comment on proposed clinical prior authorization data.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii. Presentation of utilization and clinical information	Dr. Jeffery detailed the new product in the class, Zeposia, a new oral treatment for relapsing forms of multiple sclerosis (MS). Dr. Jeffery highlighted two clinical trials where Zeposia was compared to Avonex, and Zeposia was shown to be superior. Dr. Jeffery pointed out that no claims have been received for Zeposia. Dr. Jeffery outlined the proposed criteria of a diagnosis requirement, a trial of two of the more established therapies and prescribed by or in consultation with a neurologist.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>Dr. Lim stated Anthem does not have any utilization and approved the criteria as presented.

Dr. Bitton stated HPN does not have any utilization and approved the criteria as presented.

Mr. Beranek suggested adding a maximum dose of one capsule per day, an age limit of 18 years of age or older, an EDSS Score requirement, and stated SilverSummit had not had any utilization.</td><td></td></tr>
<tr><td>iii. Discussion by Board and review of utilization data.</td><td>Board Member England discussed the benefits of requiring an EDSS score to help determine which treatment may be considered a treatment failure.

Ms. Long asked the Board to consider the criteria and what kind of information can be collected for prior authorization processing.

Board Member Adeolokun commented about the difficulty of adding an EDSS score requirement due to the variable nature of MS symptoms and recommended leaving the criteria as presented.

Board Member England agreed with the comments and suggested continued monitoring of utilization in the class.</td><td>Chairwoman Wheeler asked for the utilization of multiple sclerosis agents to be brought back to the DUR Board in October 2021.</td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria</td><td>Board Member Canty moved to approve and adopt the criteria as presented, and Board Member Adeolokun seconded.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Wheeler, Jennifer, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Adeolokun, Netochi, Pharm.D. – Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Canty, Mark, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>England, Dave, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Owens, Michael, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Tran, Jim, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
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Agenda Item	Record	Notes
c. For Possible Action: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for gonadotropin-releasing hormone (GnRH)/luteinizing hormone-releasing hormone (LHRH) antagonists and combinations.		
i. Public Comment on proposed clinical prior authorization data.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Jenna Gianninoto of Abbvie Medical Affairs, offering to answer any questions the Board may have. Ms. Woodrum reminded the public that due to open meeting laws, the public may have up to three minutes to provide public testimony but should not be used for engaging the Board in a back and forth dialog. No further public comment was offered.	
ii. Presentation of utilization and clinical information	Dr. Jeffery outlined the two products containing Elagolix, Orilissa, and Oriahnn, including the indication of endometriosis and heavy menstrual bleeding associated with uterine fibroids and the limit of duration of therapy between six months and two years due to irreversible bone loss. Dr. Jeffery discussed the low utilization of the two products and presented the proposed criteria to include the indication, a trial, or consideration for other standard therapy options or surgical ablation and limited to the approved duration of therapy. Dr. Lim agreed with the presented criteria and stated they had very few claims.	

Agenda Item	Record	Notes
	Dr. Bitton agreed with the presented criteria and stated very low utilization. Mr. Beranek suggested adding an age limit of greater than or equal to 18 years of age, a max dose of 400mg per day, a consultation with a gynecologist, failure of a non-steroidal anti-inflammatory agent, and the member does not have osteoporosis. He also discussed the low claim volume.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked the Board for comments. No comments from the Board were offered.	
iv. Proposed adoption of updated prior authorization criteria	Board Member Adeolokun moved to approve and adopt the criteria as presented by Optum, and Board Member Canty seconded. A vote was held: Wheeler, Jennifer, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adeolokun, Netochi, Pharm.D. – Vice Chair: Yes ☒ No ☐ Abst. ☐ Canty, Mark, MD: Yes ☒ No ☐ Abst. ☐ England, Dave, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Owens, Michael, MD: Yes ☒ No ☐ Abst. ☐ Tran, Jim, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
d. For Possible Action: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for bone density regulators.		
i. Public Comment on proposed clinical	The following written public comment is attached hereto:	Board Member Le, Brian, DO joined the meeting at 1:51 p.m.

Agenda Item	Record	Notes
prior authorization data.	Undated document from Amgen titled, "Clinical Value of EVENITY for the Treatment of Women with Postmenopausal Osteoporosis at High Risk for Fracture" 1. Undated document from Amgen titled, "Prolia (denosumab) Injection Clinical Fact Sheet" The public comment referenced above was highlighted on the record for members of the Board by Chairwoman Wheeler. Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Ben Droese with Amgen Medical Affairs offering comment on Evenity and Prolia. Mr. Droese highlighted the indication of Evenity, the boxed warning listed in the package insert, the mechanism of action, clinical studies demonstrated significant improvement compared to teriparatide. Mr. Droese pointed out the guidelines from the American Association of Clinical Endocrinologists recommend Evenity as initial treatment and asked the board to consider removing the requirement of Tymlos or Forteo prior to using Evenity. No further public comment was offered.	
ii. Presentation of utilization and clinical information	Dr. Jeffery outlined the different sub-categories of the medications in the class but are all indicated for the treatment of osteoporosis. Dr. Jeffery discussed the clinical trials that demonstrate all the products in the class are effective when used according to indication, and the bisphosphonates are still first-line due to efficacy, tolerability, and cost. Dr. Jeffery highlighted the place of service of the different products, Forteo and Tymlos, as once-daily subcutaneous injections given at home, Prolia is every six months administered by a health-care professional, and Evenity is a once-monthly subcutaneous injection administered by a health-care professional. Dr. Jeffery discussed the utilization and highlighted Prolia being the most utilized in the class, but none of the products have high utilization. Dr. Lim stated utilization was low and agreed with the proposed criteria.	

Agenda Item	Record	Notes
	Dr. Bitton highlighted Forteo is the most utilized product in the class and agreed with the proposed criteria. Mr. Beranek agreed with the proposed criteria, and stated utilization was very low for the class.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked the Board for comments on the proposed criteria. Dr. Jeffery displayed the criteria as included in the DUR Meeting Binder. No comments from the Board were offered.	
iv. Proposed adoption of updated prior authorization criteria	Board Member Owens moved to approve and adopt the criteria as presented, and Board Member Adeolokun seconded. A vote was held: Wheeler, Jennifer, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adeolokun, Netochi, Pharm.D. – Vice Chair: Yes ☒ No ☐ Abst. ☐ Canty, Mark, MD: Yes ☒ No ☐ Abst. ☐ England, Dave, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Le, Brian, DO: Yes ☒ No ☐ Abst. ☐ Owens, Michael, MD: Yes ☒ No ☐ Abst. ☐ Tran, Jim, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
5. Public Comment on any DUR Board Requested Report	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
6. DUR Board Requested Reports		
a. For Possible Action: Opioid utilization – top	Dr. Jeffery presented the opioid trend report as displayed by the morphine equivalent dose (MED), the count of claims continues to decrease, and the total MED quantities are trending down. Dr. Jeffery moved to the top ten	

Agenda Item	Record	Notes
prescribers and members.	members adding the top members are on fentanyl patches adding to the high MED. Dr. Jeffery displayed the top opioid prescribers, highlighted that most are pain specialists, and discussed the MED divided by the day supply. Dr. Lim described the displayed report with the claim and member counts, the sum of MEDs, and the calculated MED per day. Dr. Lim highlighted the difference between the quarters reported with a positive trend starting in the second quarter of 2020. Dr. Lim discussed the top ten prescribers, including the total MED and the MED per day supply. Dr. Lim moved to the top ten-member report discussion and highlighted the process of investigating outliers. Dr. Bitton described the opioid trend report showing a slight decrease in total MED. The top ten prescribers are mostly pain management. Dr. Bitton highlighted the top members and the consistency over the quarters. Mr. Beranek pointed out the recent increase of MED per day supply in June and the claim and member count increasing due to enrollment increasing overall. Mr. Beranek discussed the top opioid prescribers and highlighted a new prescriber in the top ten, but the rest remain consistent over the quarters. Mr. Beranek commented on the consistency of the top ten utilizers and nothing abnormal to identify.	
i. Discussion by the Board and review of utilization data.	Chairwoman Wheeler asked for comment from the Board. No comment was offered.	
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.	The Board made no requests.	
b. For Possible Action: Opioid utilization in	Dr. Jeffery presented the report and highlighted the three charts showing members on an opioid alone, members on a benzodiazepine alone, and	

Agenda Item	Record	Notes
combination with benzodiazepines.	members on a combination of the two and pointed to the decreasing member count in the combination chart. Dr. Lim commented that the Anthem utilization patterns were consistent with the number of unique members on a combination of benzodiazepines and opioids. Dr. Bitton identified a slight increase in the use of benzodiazepines recently, possibly due to the COVID-19 pandemic, while opioid utilization is slightly decreased. Mr. Beranek corrected the displayed chart; Quarter 1 should be 860 members, and Quarter 2 should be 927 members and commented on the consistency over time. Dr. Jeffery asked Mr. Beranek about the apparent high use of buprenorphine and naloxone compared to other programs. Mr. Beranek replied the use is likely due to the specific mixture of providers contracted with SilverSummit Health Plan.	
i. Discussion by the Board and review of utilization data.	Chairwoman Wheeler asked for comment from the Board. No comment was offered.	
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.	The Board made no requests.	
c. For Possible Action: Gabapentin and pregabalin utilization	Dr. Jeffery commented on the displayed report and the steady utilization of gabapentin and pregabalin over the past year and highlighted July 2019 when pregabalin generic was approved. Dr. Jeffery asked Board Member Tran if this is the information and the results he wanted to see. Board Member Tran replied the data is good, and the trend does not appear to indicate abuse.	

Agenda Item	Record	Notes
	Dr. Lim highlighted Anthem's steady use of gabapentin and the slow monthly increase of pregabalin due to the medication's expanding use. Dr. Bitton called out the slow increase of pregabalin in the Health Plan of Nevada as well and is likely due to augmenting pain therapy combined with opioids. Mr. Beranek commented on SilverSummit's utilization and that it is similar to the other programs with flat utilization and no abnormalities.	
i. Discussion by the Board and review of utilization data.	Chairwoman Wheeler asked for comment from the Board. No comment was offered.	
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.	Ms. Long asked the board to consider what reports related to the specialty pharmacy program would be beneficial and reminded the Board that the three classes are Intravenous Immune Globulin (IVIG), hepatitis C treatment, and hemophilia treatment. Dr. Jeffery suggested including specialty pharmacy reports be presented to the DUR Board starting with the July 2021 meeting that would include the first quarter of 2021.	
7. Public Comment on any Standard DUR Report	Chairwoman Wheeler asked if public comment was required at this time. Ms. Long replied that public comment is not needed for the Standard DUR Reports. No public comment was offered.	
8. Standard DUR Reports		
a. Review of Prescribing Program/Trends		
i. Top 10 Therapeutic Classes for Q1 2020 and Q2 2020 (by Payment and by Claims).	Dr. Jeffery called out the anticonvulsants and albuterol as being toward the top by claims count and expected to see an increase in albuterol use due to poor air quality. Hemophilia and HIV treatments continue to hold the top when sorted by the payment amount.	

Agenda Item	Record	Notes
	Dr. Lim pointed out the top classes by paid amount are similar to previous quarters, with HIV drugs, anti-TNF, and antipsychotics at the top while some diabetic classes are moving around toward the bottom. Dr. Lim moved to discuss the top ten by claim count and identified the increase of SSRI claims while NSAIDs decreased. Dr. Bitton pointed out the antiretrovirals, insulin, and anti-TNF products at the top of the list by paid amount, which is consistent with previous quarters, and the NSAID and albuterol changed top spots from quarter one to quarter two on the report by claim count while the opioids continue to drop lower on the list. Mr. Beranek identified how similar the reports from SilverSummit are compared to the other programs and highlighted the same classes of NSAIDs and albuterol utilization with the downward trend of opioids.	
b. Concurrent Drug Utilization Review (ProDUR)		
i. Review of Q2 2020. ii. Review of Top Encounters by Problem Type	Dr. Jeffery identified the top interventions are drug-drug interactions and duplicate therapy, with the savings summary shown for claims that were rejected or reversed. Dr. Lim pointed out the top encounters included drug-drug interactions. Dr. Bitton summarized the report displayed and reported nothing out of the ordinary. Mr. Beranek highlighted the top interventions of therapeutic duplication and early refill and reported this is consistent with previous reports.	
c. Retrospective Drug Utilization Review (RetroDUR)		
i. Status of previous quarter	Dr. Jeffery highlighted two programs that were recently performed-diabetic members without a statin and Hepatitis C treatment follow-up.	

Agenda Item	Record	Notes
ii. Status of current quarter iii. Review and discussion of responses	Dr. Lim highlighted one initiative for asthma control, where the responses were positive. Dr. Bitton discussed the different retroDUR programs and spoke about the positive results from the cardiac gaps in care and the utilization program. Mr. Beranek identified their antidiabetic non-adherence programs with positive responses and outcomes and mentioned other effective programs such as diabetic underuse of ACE inhibitors and ARB's, and opioid benchmark letters to high opioid prescribers.	
9. Public Comment on any Annual Drug Utilization Review Surveys	Chairwoman Wheeler called on Ms. Long to provide an overview of the Annual Drug Utilization Review Surveys. No public comment was offered.	
10. Centers for Medicare and Medicaid Services (CMS) Annual Drug Utilization Review Surveys	Ms. Long presented an overview of the presentations from each of the programs, asked for a high-level overview of the survey since it is long and sometimes repetitive, and referred the public to the DHCFP website for these presentations. Ms. Long asked the Board to look for ideas for future reports and initiatives.	
a. Fee-for-Service Annual DUR Survey Presented by OptumRx	Dr. Jeffery started with an overview including 186,000 members enrolled for the fiscal year 2019 and the prospective DUR criteria set by Medispan and the retroDUR program managed by OptumRx. Dr. Jeffery highlighted the effective retroDUR initiative of diabetic patients without a statin prescribed and buprenorphine use with opioids. Dr. Jeffery pointed out the brand dispense rates and the preferred drug list that sometimes prefers brand medications due to rebates.	
b. Anthem Blue Cross Blue Shield Healthcare Solutions Annual DUR Survey presentation	Dr. Lim summarized the retroDUR activities for the year, highlighting two successful programs consisting of polypharmacy and morphine equivalent dose programs, and commented on the other programs available such as the controlled substances management program and coordination of care program.	

Agenda Item	Record	Notes
c. Health Plan of Nevada (HPN) Annual DUR Survey presentation	Dr. Bitton presented an overview, including the use of Medispan for the DUR criteria with internal meeting groups to assess new programs such as therapeutic duplication and cumulative high dose initiatives. Dr. Bitton reported the effectiveness of the program leads to better care and reduced cost by reducing duplicate therapy. Dr. Bitton mentioned the required changes as a result of the SUPPORT act, including the use of opioids while on medication assisted therapy (MAT) or looking at antipsychotic use in children.	
d. SilverSummit Healthplan Annual DUR Survey presentation	Mr. Beranek highlighted the quality of care delivered to members through their retroDUR program, such as hyperlipidemia adherence and diabetic medication adherence, and pointed out the top ten prior authorization requests. Mr. Beranek pointed out the generic dispense rate of close to 90%.	
11. Closing Discussion		
a. Public comment	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
b. For Possible Action: Date and location of the next meeting.	Chairwoman Wheeler stated the next meeting is scheduled for January 28, 2021, with a location that is yet to be determined.	
c. Adjournment	The meeting was adjourned at 3:12 p.m.	

Attachment A – Members of the Public in Attendance

Jean Ritter, Zealand Pharmaceuticals
Jenna Gianninoto, Abbvie
Ben Droese, Amgen
Lovell Robinson, Abbvie
Susan Hertzberg, Genentech
Joe Germain, Biogen
Joe Ferroli, Takeda
Gary Okano, BMS
Chi Kohlhoff, Viela Bio
Warner Quon, Ascendis
Leann McAllister, Nevada Chapter, American Academy of Pediatrics
Kelvin Yamashita, Sanofi
Jeana Colabianchi, Sunovion
Dave Peightal, Dolcrx
Mike Finklein, Otsuka
Sean Staff
Kaysen Bala, Biogen
Melissa Sommers, Novartis
Chris Gilbert, Genentech
Michelle Duke, Genentech
Hector Mobine, Amgen
Dawn Dynak, Gilead

Attachment B – Submitted Written Comment


Prolia Clinical Fact Sheet.pdf


EVENITY Clinical Value Fact Sheet.pd

Clinical Presentations

Prior Authorization Guideline

Guideline Name Fintepla (fenfluramine)

1 . Indications

Drug Name: Fintepla (fenfluramine)
Dravet Syndrome Indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

2 . Criteria

Product Name: Fintepla	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of seizures associated with Dravet syndrome	

AND **2** - Prescribed by or in consultation with a neurologist

Product Name: Fintepla	
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Documentation of positive clinical response to therapy	

3 . References

1. Fintepla Package Insert. Zogenix Inc. Emeryville, CA. June 2020.

Nevada Medicaid

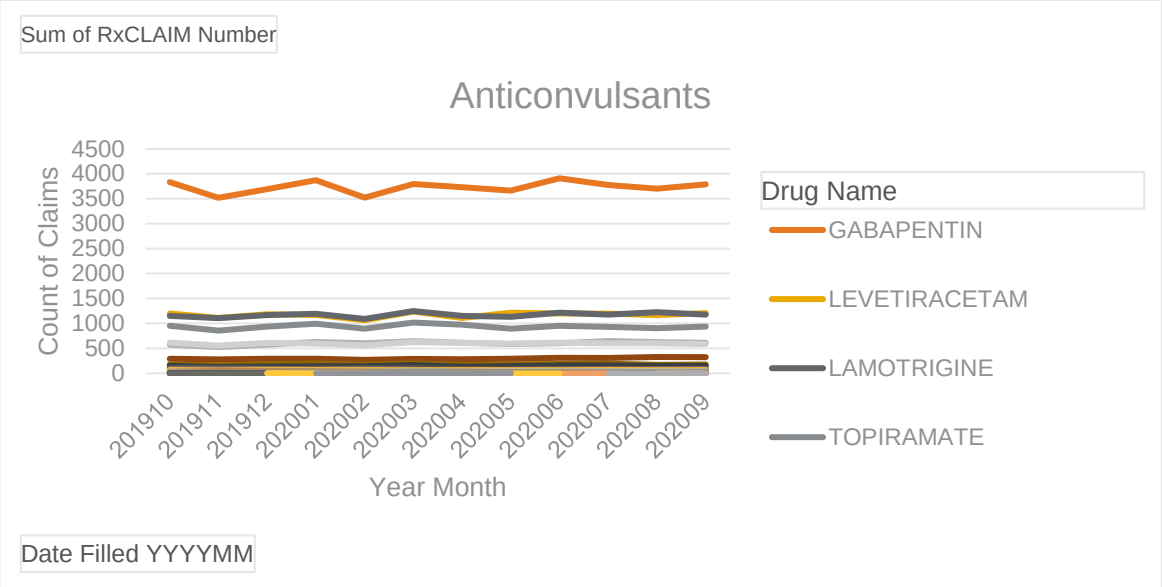
Anticonvulsants – Miscellaneous

Fee for Service

October 1, 2019 – September 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
APTIOM	40	317	10,116	15,115
TOPAMAX SPRINKLE	6	21	750	3,330
SUBVENITE	3	3	32	62
LAMOTRIGINE ODT	60	270	9,502	20,708
LAMOTRIGINE STARTER KIT	1	1	35	49
TOPIRAMATE ER	34	162	5,158	7,859
VIMPAT	438	3,544	87,010	366,056
CARBAMAZEPINE ER	169	1,037	34,405	91,304
LAMICTAL ODT	8	21	895	925
LAMOTRIGINE ER	133	779	26,500	43,500
NEURONTIN	14	25	524	2,959
CARBATROL	4	13	509	1,797
LAMICTAL XR	10	53	1,850	2,420
TRILEPTAL	15	82	2,634	31,000
LEVETIRACETAM	2,252	14,058	413,912	2,578,682
GABAPENTIN	8,919	44,813	1,463,263	4,632,329
LAMICTAL CHEWABLE DISPE	2	16	471	6,092
SUBVENITE STARTER KIT/OF	1	1	49	49
KEPPRA XR	10	49	1,797	7,331
LEVETIRACETAM/SODIUM CH	7	8	8	900
EPITOL	13	15	510	1,110
QUDEXY XR	21	161	5,465	7,715
BANZEL	40	393	12,183	169,448
LEVETIRACETAM ER	65	357	11,123	30,904
DIACOMIT	1	1	30	60
TROKENDI XR	23	120	4,320	7,590
TOPAMAX	8	25	870	1,620
BRIVIACT	70	399	12,430	35,596
ZONEGRAN	2	13	334	1,900
OXTELLAR XR	12	86	2,939	4,093
PREGABALIN	1,404	7,230	208,659	518,490
TEGRETOL	4	8	240	1,380
TOPIRAMATE	2,132	11,232	379,419	761,442
PRIMIDONE	134	674	23,923	60,098
LAMICTAL	103	289	2,916	10,228
KEPPRA	22	186	6,738	92,320
EPIDIOLEX	81	721	22,395	123,566
ZONISAMIDE	274	1,726	59,001	191,582
LAMOTRIGINE	2,306	14,025	451,584	896,160
LAMICTAL STARTER/NOT TA	1	1	30	49
OXCARBAZEPINE	1,143	7,158	219,439	725,174
CARBAMAZEPINE	417	2,155	71,128	283,629

LYRICA	275	852	14,933	37,100
MYSOLINE	1	11	330	870
TEGRETOL-XR	4	42	1,173	3,544



BBBB. Anticonvulsants

Therapeutic Class: Anticonvulsants
Last Reviewed by the DUR Board: January 23, 2020

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

1. Cannabinoid

   a. Epidiolex® (cannabidiol)

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

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

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

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

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

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

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

      2. Recertification Request

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

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

      3. Prior Authorization Guidelines

         a. Initial prior authorization will be for three months.

         b. Recertification approval will be for 12 months.

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

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

2. Nayzilam® (midazolam)

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

1. The recipient has a diagnosis of acute intermittent seizures; and

2. The recipient is at least 12 years of age; and

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

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

b. Recertification Request (the recipient must meet all criteria)

1. Documentation of positive clinical response to Nayzilam® therapy.

c. Prior Authorization Guidelines

1. Initial prior authorization will be for six months.

2. Recertification approval will be for 12 months.

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

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation Greater Chicago 2020*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation Greater Chicago 2020*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannabidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It was the first FDA-approved drug for treatment of patients with Dravet syndrome and the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. In July 2020, cannabidiol was FDA-approved for the treatment of seizures associated with tuberous sclerosis complex (TSC) in pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020, FDA news release 2020)*. The age range for the indications of treatment of seizures associated with LGS or Dravet syndrome was also expanded to include pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020)*. Initially designated as a schedule V controlled substance, cannabidiol has been descheduled and is no longer classified as a controlled substance.
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. In June 2020, fenfluramine oral solution (Fintepla) was approved for the same indication without the requirement for concomitant clobazam (*Fintepla prescribing information 2020*).
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with TSC. This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-

Drug	Generic Availability
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Fenfluramine (Fintepla)	-
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	- ¶¶
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon†, Depakene†)	✔
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film
¶¶ Generic product has been FDA-approved, but not currently marketed

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

INDICATIONS

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

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

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

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

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

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

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

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

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

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

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS, Dravet syndrome, or TSC in patients ≥ 1 year of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures (petit mal) do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
  - Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age
- Divalproex sodium:

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

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

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

- Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Prophylaxis of migraine headache in patients ≥ 12 years of age

- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

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

CLINICAL EFFICACY SUMMARY

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

- As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Oxcarbazepine is potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- As initial monotherapy for children with newly diagnosed or untreated absence seizures:
  - Ethosuximide and valproate are established as efficacious/effective.
  - Lamotrigine is possibly efficacious/effective.
  - Gabapentin is established as inefficacious/ineffective.
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
- As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
  - Carbamazepine and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
- For patients with newly diagnosed JME:
  - Topiramate and valproate are potentially efficacious/effective.
  - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
- There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.

- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
  - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
    - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
    - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
    - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
  - For the secondary outcome, time to first seizure:
    - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
    - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
  - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
  - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
  - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50;

95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) vs levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments.

Cannabidiol, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al 2018; Devinsky et al 2017*). In July 2020, cannabidiol was FDA-approved for a third indication, treatment of seizures associated with TSC, and the age range for all 3 indications was aligned to include pediatric patients 1 year of age and older (*FDA news release 2020, Epidiolex prescribing information 2020)*. In a placebo-controlled trial of 224 patients with TSC and seizures inadequately controlled with ≥ 1 concomitant AED, cannabidiol resulted in a significant reduction in seizure frequency compared to placebo (*Epidiolex prescribing information 2020*). To date, no comparative trials have been published.

- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- In June 2020, the FDA approved a third drug, fenfluramine (Fintepla), for use in the treatment of seizures associated with Dravet syndrome. Two randomized, double-blind, placebo-controlled studies evaluated fenfluramine in patients 2 to 18 years of age with Dravet syndrome who were inadequately controlled with 1 to 4 other AEDs. In both trials, fenfluramine significantly reduced the frequency of convulsive seizures occurring in a 28-day period as compared to placebo. In the first trial, in patients not receiving stiripentol, fenfluramine at a dose of 0.7 mg/kg/day demonstrated a 62.3% greater reduction in mean monthly convulsive seizure frequency (MCSF) over 14 weeks compared with placebo. In the second trial, in patients who were receiving a stiripentol-inclusive AED regimen, fenfluramine at a dose of 0.4 mg/kg/day showed a 54% greater reduction in MCSF over 15 weeks compared with placebo (*Fintepla package insert 2020, Lagae et al 2020, Nabbout et al 2019*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).
- A meta-analysis of 9 randomized controlled trials evaluated the efficacy and safety of levetiracetam vs phenytoin as second-line treatment for benzodiazepine-resistant status epilepticus in children and adults. The efficacy outcomes included seizure cessation and seizure recurrence within 24 hours. The authors did not find a significant difference in efficacy between levetiracetam and phenytoin in the overall population or in the subgroup analysis of pediatric patients. AEs were similar across both groups except for a higher incidence of cardiac instability, reported mainly as hypotension, in the phenytoin group (*DeMott et al 2020).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate,

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

- Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
- Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.

▪ As monotherapy in patients with TRAFE:
- Eslicarbazepine use may be considered to decrease seizure frequency.
- Data are insufficient to recommend use of second- and the other third-generation AEDs.

▪ For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.

▪ Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.

▪ For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
- Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
- Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
- Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
- Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.

▪ The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.

        - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
        - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
        - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
        - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
    - For treatment in the pediatric population, conclusions included the following:
        - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
        - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
        - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
        - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.

        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
    - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
    - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
    - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
    - Recommendations/findings include the following:
        - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
        - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
        - Treatment options with established or probable efficacy include the following:
            - Focal seizures: levetiracetam
            - Epileptic spasms: High-dose or low-dose ACTH
            - Dravet syndrome: stiripentol
        - Treatment options with possible efficacy include the following:
            - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
            - Epileptic spasms: prednisone, vigabatrin
            - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
            - Dravet syndrome: topiramate, zonisamide, valproate
            - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
            - Provoked or situational seizures: carbamazepine
        - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
    - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
    - Recommendations include the following:
        - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.

        - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
        - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
        - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
        - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
    - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
    - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
    - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
    - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
  - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).

- Common AEs among AEDs include the following (*Fintepla prescribing information 2020, Schachter 2019*):
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol, fenfluramine)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, fosphenytoin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, tiagabine, topiramate, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
  - cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
  - abnormal magnetic resonance imaging signals in infants (vigabatrin)
  - intramyelinic edema (vigabatrin)
  - serotonin syndrome (fenfluramine)
  - significant elevation in blood pressure including hypertensive crisis (fenfluramine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

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

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fenfluramine:
  - Use of serotonergic drugs with 5-HT2B receptor agonist activity (eg, fenfluramine) is associated with valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with fenfluramine, and the benefits vs risks of initiating or continuing treatment with this product must be considered based on echocardiogram findings.
  - Due to the risks of valvular heart disease and pulmonary arterial hypertension, fenfluramine is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe fenfluramine and pharmacies that dispense the product must be certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic cardiovascular monitoring is performed and report any AE suggestive of valvular heart disease and/or pulmonary hypertension to the fenfluramine REMS program.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.

- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a REMS program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several AEs.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Fenfluramine (Fintepla)	oral solution	oral	2 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT,	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lamictal XR, Subvenite)				
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene†, Depacon†)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

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

CONCLUSION

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

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Prior Authorization Guideline

Guideline Name Evrysdi (risdiplam)

1 . Indications

Drug Name: Evrysdi (risdiplam)
Spinal Muscular Atrophy Indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

2 . Criteria

Product Name: Evrysdi	
Diagnosis	Spinal Muscular Atrophy
Approval Length	12 Months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of spinal muscular atrophy (SMA) Type I, II, or III [1-3, A]

AND

2 - Both of the following: [1-7]

2.1 The mutation or deletion of genes in chromosome 5q resulting in one of the following: [B]

2.1.1 Homozygous gene deletion or mutation (e.g., homozygous deletion of exon 7 at locus 5q13)

OR

2.1.2 Compound heterozygous mutation (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 [allele 2])

AND

2.2 Patient has at least 2 copies of SMN2 [C]

AND

3 - Patient is not dependent on both of the following: [2-3, D]

- Invasive ventilation or tracheostomy
- Use of non-invasive ventilation beyond use for naps and nighttime sleep

AND

4 - Patient is at least 2 months of age or older [1]

AND

5 - At least one of the following exams (based on patient age and motor ability) has been conducted to establish baseline motor ability*: [2-7, E]

- Hammersmith Infant Neurological Exam (HINE) (infant to early childhood)
- Hammersmith Functional Motor Scale Expanded (HFMSE)
- Upper Limb Module (ULM) Test (Non ambulatory)
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Motor Function Measure 32 (MFM-32) Scale

AND

6 - Prescribed by or in consultation with a neurologist with expertise in the diagnosis and treatment of SMA

AND

7 - Patient is not to receive concomitant chronic survival motor neuron (SMN) modifying therapy for the treatment of SMA (e.g., Spinraza) [2-3, 10, F]

AND

8 - One of the following: [2-3, 10, F]

8.1 Patient has not previously received gene replacement therapy for the treatment of SMA (e.g., Zolgensma)

OR

8.2 Both of the following:

- Patient has previously received gene therapy for the treatment of SMA (e.g., Zolgensma)
- Provider attests that there has been an inadequate response to gene therapy (e.g., sustained decrease in at least one motor test score over a period of 6 months)

Notes	*Baseline assessments for patients less than 2 months of age requesting risdiplam proactively are not necessary in order to not delay access to initial therapy in recently diagnosed infants. Initial assessments shortly post-therapy can serve as baseline with respect to efficacy reauthorization assessment.

Product Name: Evrysdi	
Diagnosis	Spinal Muscular Atrophy
Approval Length	12 Months
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of positive clinical response to therapy from pretreatment baseline status as demonstrated by the most recent results from one of the following exams:

1.1 One of the following HINE-2 milestones: [2]

- Improvement or maintenance of previous improvement of at least a 2 point (or maximal score) increase in ability to kick
- Improvement or maintenance of previous improvement of at least a 1 point increase in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp
- Patient exhibited improvement, or maintenance of previous improvement in more HINE motor milestones than worsening, from pretreatment baseline (net positive improvement)
- Patient has achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

OR

1.2 One of the following HFMSE milestones: [8]

- Improvement or maintenance of a previous improvement of at least a 3 point increase in score from pretreatment baseline
- Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

OR

1.3 One of the following ULM test milestones: [2, 8-9]

- Improvement or maintenance of a previous improvement of at least a 2 point increase in score from pretreatment baseline
- Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

OR

1.4 One of the following CHOP INTEND milestones: [2]

- Improvement or maintenance of a previous improvement of at least a 4 point increase in score from pretreatment baseline
- Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

OR

1.5 One of the following MFM-32 milestones: [2]

- Improvement or maintenance of a previous improvement of at least a 3 point increase in score from pretreatment baseline
- Patient has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk)

AND

2 - Patient continues to not be dependent on both of the following: [2-3, D]

- Invasive ventilation or tracheostomy
- Use of non-invasive ventilation beyond use for naps and nighttime sleep

AND

3 - Prescribed by or in consultation with a neurologist with expertise in the diagnosis and treatment of SMA

AND

4 - Patient is not to receive concomitant chronic survival motor neuron (SMN) modifying therapy for the treatment of SMA (e.g., Spinraza) [2-3, 10, F]

AND

5 - One of the following: [2-3, 10, F]

5.1 Patient has not previously received gene replacement therapy for the treatment of SMA (e.g., Zolgensma)

OR

5.2 Both of the following:

- Patient has previously received gene therapy for the treatment of SMA (e.g., Zolgensma)
- Provider attests that there has been an inadequate response to gene therapy (e.g., sustained decrease in at least one motor test score over a period of 6 months)

3 . Endnotes

A. There were two major Phase 2/3 trials that the FDA assessed when determining Evrysdi's clinical efficacy and subsequent approval (SUNFISH and FIREFISH). SUNFISH only enrolled patients with SMA Types 2 and 3 and FIREFISH only enrolled patients with SMA Type 1. [2-3]
B. This is the definition that the clinical trials SUNFISH and FIREFISH used. Also consistent with clinical guidelines. [2-7]
C. FIREFISH required patients to have 2 copies of SMN2, and SUNFISH only enrolled patients with 2-4 copies of SMN2. [2-3]
D. Invasive ventilation or tracheostomy was an exclusion criteria in both the SUNFISH and FIREFISH trials. Use of non-invasive ventilation beyond use for naps and nighttime sleep was only an exclusion criteria in FIREFISH. [2-3]
E. MFM-32 was included in Evrysdi criteria but not Spinraza because Spinraza did not study MFM-32 as an endpoint. Baseline motor score standards was only used as an inclusion criterion for SUNFISH. Revised upper limb module (RULM) entry item A (Brooke score) equal to or greater than 2 AND MFM-32 (Item 9) scores equal to or greater than 1 were required. As this was only for the SUNFISH trial and only applied to some of the motor scores, it was deemed unnecessary to include as a criterion. [2]
F. A recent European ad-hoc consensus statement on SMA stated that there currently is no published evidence that the combination of two disease modifying therapies (e.g., Evrysdi and Zolgensma) is superior to any single treatment alone. Both FIREFISH and SUNFISH excluded patients that were on concomitant or previous treatment with either SMN2-targeting antisense oligonucleotide, or gene therapy (e.g., Spinraza or Zolgensma). JEWELFISH is an ongoing open label phase 2 trial that included patients previously treated with another SMA targeted therapy (e.g., Zolgensma, Spinraza). JEWELFISH is scheduled to be completed in December 2024. [2-3,10-11]

4 . References

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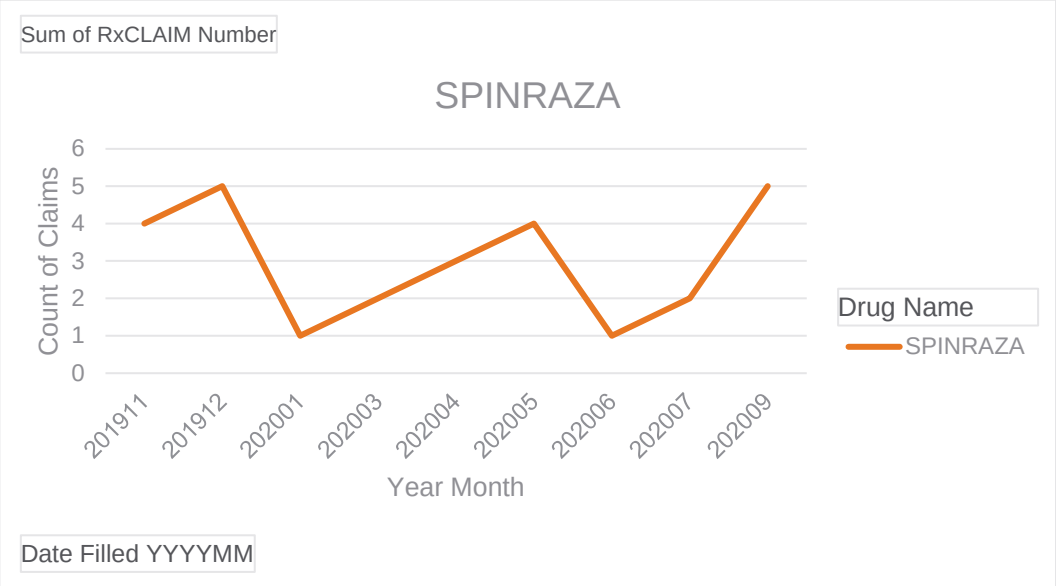
Nevada Medicaid

Spinal Muscular Atrophy (SMA) Agents

Fee for Service

October 1, 2019 – September 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
SPINRAZA	10	27	1248	135



NNN. Spinraza® (nusinersen)

Therapeutic Class: Spinraza® (nusinersen)
Last Reviewed by the DUR Board: August 24, 2017

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

1. Coverage and Limitations

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

   a. Initial request:

      1. The recipient has a diagnosis of Spinal Muscular Atrophy (SMA), and

      2. The medication is prescribed by or in consultation with a neurologist who has experience treating SMA.

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

      1. The recipient has been on therapy for less than 12 months; and

      2. The recipient is maintaining neurological status; and

      3. The recipient is tolerating therapy; and

      4. The medication is prescribed by or in consultation with a neurologist who has experience treating SMA, or all of the following:

         a. The recipient has been on therapy for 12 months or more; and

         b. The recipient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients); and

         c. The recipient is maintaining neurological status; and

         d. The recipient is tolerating therapy; and

         e. The medication is prescribed by or in consultation with a neurologist who has experience treating SMA.

2. Prior Authorization Guidelines

   a. Prior authorization approvals will be for:

      1. Initial request: 12 months.

2. Recertification request: continued use shall be reviewed at least every 12 months.

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

K. Zolgensma (onasemnogene abeparvovec-xioi)

Therapeutic Class: Spinal Muscular Atrophy Agents
Last Reviewed by the DUR Board: October 17, 2019

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

1. Coverage and Limitations

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

a. The recipient must be two years of age or younger; and

1. The recipient must have the mutation or deletion of genes in chromosome 5q in one of the following: homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); or

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

a. The recipient has a diagnosis symptomatic Type I or Type II SMA confirmed by a neurologist with expertise in the diagnosis of SMA; or

b. The recipient has a diagnosis of SMA based on the results of SMA newborn screening with three copies or less of Survival of Motor Neuron 2 (SMN 2); and

3. The recipient is not dependent on either invasive ventilation or tracheostomy or 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 the recipient's anti-AAV9 antibody titers are less than or equal to 1:50; and

5. The recipient is not to receive concomitant SMN modifying therapy (e.g. Spinraza®); and

6. The medication is prescribed by a neurologist with expertise in the diagnosis of SMA; and

7. The recipient has never received Zolgensma® treatment in their lifetime.

2. Prior Authorization Guidelines

   a. Prior authorization approvals will be for a one time authorization in lifetime.

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

Therapeutic Class Overview
Spinal Muscular Atrophy (SMA) Agents

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons in the spinal cord and brainstem, leading to progressive muscular atrophy and weakness (*Genetics Home Reference 2020, Mercuri et al 2018[a]*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant mortality (*Bodamer 2020*).
- SMA is an autosomal recessive inherited disorder. The overall incidence is between 4 and 10 per 100,000 live births, and 1 person in 50 to 90 is a carrier of a mutation that can cause SMA (*Bodamer 2020*).
- The *SMN1* gene is responsible for the production of SMN protein, which is ubiquitously expressed in all cells throughout fetal and post-natal development. Deletion or mutations in the *SMN1* gene lead to a shortage of the protein. Without this protein, motor neurons degenerate and nerve impulses are not carried between the brain and muscles, resulting in characteristic muscle weakness and impaired movement (*Bodamer 2020, Finkel et al 2018, Genetics Home Reference 2020*).
  - There is also a modifying (or "backup") gene called *SMN2*, which generates a smaller amount of functional SMN protein. The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have a less severe SMA type *(Bodamer 2020, Calucho et al 2018*).
- There are several forms of SMA with varying degrees of severity and ages of onset (*Bodamer 2020, Genetics Home Reference 2020, Glascock et al 2018, , Rao et al 2018*).
  - In SMA type 1, untreated patients have severe weakness and hypotonia and never gain the ability to sit unsupported. Patients with SMA type 1 typically have an onset of symptoms between the age of 0 and 6 months, and have a typical lifespan of < 2 years without permanent ventilation.
  - Patients with SMA type 2 (intermediate), 3 (mild), or 4 (adult-onset) experience a later onset and less severe symptoms usually characterized by varying degrees of muscle weakness. Type 0 (prenatal) is the rarest and most severe form, with newborns typically living for < 6 months.
- SMA type 1 is the most common form, affecting approximately 58% of patients. Type 2 and type 3 occur in approximately 29% and 13% of patients, respectively, and type 4 is less common (< 5%) (*Food and Drug Administration [FDA] medical review 2016*). Mothers may notice a decrease of fetal movement in late pregnancy, and some experts classify prenatal onset as type 0 SMA, which is very rare (*Bodamer 2020, FDA medical review 2016*).
- Management of SMA has historically been limited to supportive measures, focusing on providing nutrition and respiratory assistance and preventing or treating the complications of weakness. Nonpharmacologic treatments include physical therapy, spinal bracing, chest physiotherapy, and respiratory support (*Bodamer 2020, Finkel et al 2018, Mercuri et al 2018[a]).*
- In December 2016, Spinraza (nusinersen) became the first FDA-approved product for the treatment of SMA. The FDA granted nusinersen Fast Track designation, Orphan Drug designation, and Priority Review (*FDA 2016*).
  - Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to sites within *SMN2* pre-mRNA, promoting inclusion of exon 7 in *SMN2* mRNA transcripts and increasing production of full-length, functional SMN protein (*Finkel et al 2016*).
- Zolgensma (onasemnogene abeparvovec-xioi; referred to as onasemnogene abeparvovec), approved by the FDA in May 2019, is the second FDA-approved product for the treatment of SMA. Onasemnogene abeparvovec was granted Priority Review by the FDA, and received Breakthrough Therapy, Fast Track, and Orphan Drug designations (*FDA 2019*).
  - Onasemnogene abeparvovec is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein. The virus enters the nucleus of neurons and forms an episome (a DNA molecule that replicates independently of chromosomal DNA). The episome is transcribed and translated to produce the missing SMN protein.
- Evrysdi (risdiplam), approved by the FDA in August 2020, is the third FDA-approved product for the treatment of SMA. Risdiplam was granted Priority Review by the FDA, and received Fast Track and Orphan Drug designations.
  - Risdiplam is a splicing modifier that increases exon 7 inclusion in the *SMN2* mRNA transcripts, thereby increasing production of full-length SMN protein (*Evrysdi prescribing information 2020*).

- Medispan class: Spinal Muscular Atrophy Agents
- Medispan class: Spinal Muscular Atrophy – Gene Therapy Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Evrysdi (risdiplam)	-
Spinraza (nusinersen)	-
Zolgensma (onasemnogene abeparvovec-xioi)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evrysdi (risdiplam)	Spinraza (nusinersen)	Zolgensma (onasemnogene abeparvovec-xioi)
Treatment of SMA in patients 2 months of age and older	✔		
Treatment of SMA in pediatric and adult patients		✔	
Treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene			✔ *

* Limitations of use: The safety and effectiveness of repeat administration of onasemnogene abeparvovec have not been evaluated. The use of onasemnogene abeparvovec in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

- 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

Zolgensma (onasemnogene abeparvovec-xioi)

- The safety and efficacy of onasemnogene abeparvovec were evaluated in 3 clinical trials, START, STR1VE and SPR1NT.
  - START was a phase 1, open-label trial of 15 patients with SMA type 1 who had 2 copies of *SMN2.* Two cohorts were treated: 3 patients in cohort 1 received a low dose of Zolgensma, while 12 patients in cohort 2 received a high dose of Zolgensma. After 24 months of treatment, all patients in cohort 2 were alive and none required permanent ventilation (described as ≥ 16 hours per day of required ventilatory support for 14 consecutive days in the absence of acute reversible illness or perioperative change). One patient in group 1 reached a pulmonary event at 28.8 months of age. Patients also had improvement in meeting certain motor milestones, with the majority gaining the ability to sit unassisted, roll over, and achieve head control. Gains in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) were also noted (*Al-Zaidy et al 2019*, *Mendell et al 2017)*.
    - Ten of the 12 patients in cohort 2 enrolled in the START long-term follow-up (LTFU) study. As of December 31, 2019, all 10 patients were alive and free of permanent ventilation, no previously achieved motor milestone had been lost, and 2 patients gained a new milestone of standing with assistance. There were no new treatment-related serious adverse effects (AEs) and no AEs of special interest during the LTFU study. Some of the patients in the LTFU study have received subsequent therapy with nusinersen (*Novartis 2020[a]*).
  - STR1VE was an open-label, single-arm, multicenter trial in the U.S that evaluated the safety and efficacy of Zolgensma in patients with SMA type 1 who were < 6 months of age at the time of gene therapy, with 1 or 2 copies of *SMN2* and who had bi-allelic *SMN1* gene deletion or point mutations.
    - Data as of March 8, 2019 (median duration of follow-up, 10.2 months) showed that of 20 patients who reached 10.5 months of age or discontinued the study prior to 10.5 months of age, 19 (95%) were surviving without permanent

ventilation. Of 15 patients who had reached 13.6 months of age or discontinued prior to 13.6 months, 13 (87%) were surviving without permanent ventilation (*Day et al 2019*).
    - According to updated data provided by the manufacturer in March 2020, 20 of 22 patients (91%) met the co-primary endpoint of event-free survival at 14 months, and 13 of 22 patients (59%) met the co-primary endpoint of functional sitting for ≥ 30 seconds at 18 months of age. Sustained improvements in CHOP-INTEND scores were also noted (*Novartis 2020[a]*).
  - SPR1NT is an ongoing, Phase 3, open-label, single-arm, multicenter trial designed to evaluate the safety and efficacy of Zolgensma in pre-symptomatic patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age. The primary outcome measure for patients with 2 copies of *SMN2* is independent sitting for ≥ 30 seconds by 18 months. The primary outcome measure for patients with 3 copies of *SMN2* is standing without support for at least 3 seconds by 24 months (*Avexis 2019, Strauss et al 2019)*.
    - As of December 31, 2019, 14 patients with 2 copies of *SMN2* and 15 patients with 3 copies of *SMN2* had been treated. In the 2-copy cohort, 8 patients so far were able to sit independently for ≥ 30 seconds (range, 5.7 to 11.8 months of age), and 4 patients were able to walk independently. Of the patients with 3 copies of *SMN2*, 4 patients were able to stand alone without support for ≥ 3 seconds (9.5 to 12.4 months of age) and 3 patients were able to walk independently (12.2 to 15.1 months of age). Patients in both cohorts who had not achieved these milestones yet were still within the normal age development window for these milestones (*Novartis 2020[a]*).
- Zolgensma is still being studied in a number of trials in pursuit of expanding patient populations. Of note, the STRONG trial is a Phase 1 trial investigating intrathecal delivery in children with SMA type 2 aged 6 months to 5 years (*Clinicaltrials.gov 2020*). Based on their review of data from STRONG, the FDA has notified the manufacturer that they recommend a pivotal confirmatory study to supplement the STRONG data in order to support a regulatory submission for intrathecal use (*Novartis 2020[b])*.

Spinraza (nusinersen)

- Key clinical trials supporting the safety and efficacy of nusinersen include ENDEAR, CHERISH, and NURTURE.
  - The pivotal trial ENDEAR (N = 121) was a 13-month, Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients 7 months or younger who had an onset of SMA symptoms at ≤ 6 months of age and had homozygous deletion or mutation of *SMN1* and 2 copies of the *SMN2* gene (*Finkel et al 2017).*
    - At interim analysis, a higher proportion of patients treated with nusinersen had a motor milestone response than those in the control group (41% vs 0%, p < 0.001), prompting early termination of the trial. The final analysis showed that 51% of the nusinersen-treated group had a motor milestone response, compared with no patients in the control group. Motor milestones reached included achievement of full head control (22%), ability to roll over (10%), ability to sit independently (8%), and ability to stand (1%).
    - A co-primary endpoint of event-free survival also favored nusinersen vs placebo (61% vs 32%; p = 0.005).
    - Patients in the nusinersen group also had a 63% lower risk of death compared with the control group (hazard ratio, 0.37; 95% confidence interval [CI], 0.18 to 0.77; p = 0.004).
  - CHERISH (N = 126) was a Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients aged 2 to 12 years with later-onset SMA. The primary endpoint was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score at 15 months of treatment (*Mercuri 2018[b]).*
    - In the pre-planned interim analysis, there was a significant improvement in the HFMSE from baseline to 15 months in the nusinersen group vs the control group (mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; p < 0.001).
    - Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group vs 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (p < 0.001), and the overall incidence of AEs was similar in the nusinersen group and the control group (93% vs 100%, respectively).
  - The NURTURE study is an ongoing, Phase 2, open-label, single-arm trial to evaluate the use of nusinersen in patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age and asymptomatic at the time of treatment initiation The primary endpoint was time to death or respiratory intervention (invasive or non-invasive for ≥ 6 hours per day continuously for ≥ 7 days or tracheostomy). At an interim analysis published in 2019, 25 patients had been enrolled, of whom 15 had 2 *SMN2* copies and 10 had 3 *SMN2* copies. At the time of the interim analysis, 4 participants (16%) had utilized a respiratory intervention. All patients were alive and none required permanent ventilation. Efficacy was further supported by the achievement of motor milestones by HINE-2 and motor function by CHOP-INTEND. Of note, all patients achieved the milestone of “sitting without support” and 23 of 25 patients (92%) achieved “walking with assistance” (*De Vivo et al 2019*).

- In June 2020, the manufacturer reported updated data noting that all children treated pre-symptomatically were alive and none required permanent ventilation after up to 4.8 years of continuous treatment. In addition, patients continued to maintain and make progressive gains in motor function. The study has been extended by an additional 3 years to allow the collection of continued data (*Biogen 2020*).

- The FDA-approved indication for nusinersen does not limit its use to certain ages or SMA types. The FDA medical review noted that the underlying cause of SMA (a shortage of SMN protein) is common to patients with all SMA types, and it is reasonable to expect that nusinersen should provide clinical benefits in all SMA types. Open-label studies included patients 2 to 17 years of age with 2 to 5 *SMN2* copies and symptom onset corresponding to types 2 and 3 SMA; these results plus the initial summary of the sham-controlled trial in later-onset patients support the conclusion that nusinersen provides clinical benefits to patients with types 2 and 3 SMA and allow reasonable extrapolation to these populations. Given the invasive nature of nusinersen administration, patients with milder forms of SMA (type 4) may need to weigh potential benefits, risks and discomfort, and relative symptom severity to make individual treatment decisions (*FDA medical review 2016*).

Evrysdi (risdiplam)

- Evidence for the safety and efficacy of risdiplam is available from results of 2 clinical trials, FIREFISH and SUNFISH. Both studies are still ongoing.
  - FIREFISH is a 2-part, Phase 2/3, open-label, multicenter, dose-escalation study assessing the safety and tolerability of risdiplam in infantile-onset SMA type 1 patients aged 1 to 7 months.
    - In part 1, 21 infants were assigned to group A (n = 4) receiving a low dose or group B (n = 17) recieiving a high dose that was adjusted up to the recommended dose of 0.2 mg/kg/day. Of the infants who were treated with the recommended dosage of risdiplam 0.2 mg/kg/day, 7 of 17 (41%) were able to sit independently for ≥ 5 seconds as assessed by the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) after 12 months of treatment, a milestone beyond that expected in the natural history of the disease. Additionally, 90% of patients (19/21) were alive without permanent ventilation (and reached 15 months of age or older) (*Evrysdi prescribing information 2020*). The most common AEs included pyrexia, upper respiratory tract infections, rash, diarrhea, vomiting, pneumonia and constipation (*Evrysdi AMCP Dossier 2020).*
      - The manufacturer announced 2-year data for FIREFISH part 1, noting that an estimated 88% of patients were alive and required no permanent ventilation after 2 years. Patients continued to achieve motor milestones, including 59% (10/17) sitting without support for ≥ 5 seconds, 65% (11/17) maintaining upright head control, 29% (5/17) turning over, and 30% (5/17) standing either supporting weight or with support. No new safety signals were identified (*Genentech 2020*).
    - Part 2 is a pivotal single-arm study evaluating the use of risdiplam in 41 infants with SMA type 1 for 24 months. Infants received risdiplam at a dose of 5 mg once daily for patients with a body weight ≥ 20 kg or 0.25 mg/kg for patients with a body weight < 20 kg. The primary outcome is the proportion of infants sitting without support for ≥ 5 seconds after 12 months on treatment as assessed by BSID-III. A primary analysis at 12 months (November 2019) showed that 12/41 infants (29%; 90% CI, 17.8% to 43.1%) were sitting without support for ≥ 5 seconds. After 24 months in part 2, infants will continue in a open-label extension phase (*Evrysdi AMCP Dossier 2020*).
  - SUNFISH is a 2-part, double-blind, placebo-controlled trial in children and young adults aged 2 to 25 years old with SMA type 2 and 3 (*Evrysdi AMCP Dossier 2020*).
    - Part 1 (N = 51) was a dose-finding phase evaluating safety and tolerability of risdiplam. Patients received risdiplam or placebo for a minimum of 12 weeks, followed by open-label use of risdiplam at the dose selected for Part 2. Exploratory results at 12 months showed improvements in motor function compared to natural history.
    - In Part 2, 180 patients were randomized (type 2, 71%; type 3, 29%) to risdiplam or placebo for 24 months followed by an open-label extension period. The primary endpoint was the change from baseline in motor function measure 32 scale (MFM-32) at month 12; the average baseline MFM-32 score was 45 in the risdiplam group vs 47 in the placebo group. The primary analysis showed a statistically significant 1.36-point increase from baseline MFM-32 score in the risdiplam group (95% CI, 0.61 to 2.11) compared to a -0.19-point change in the placebo group (95% CI, -1.22 to 0.84). The most common AEs that occurred in > 10% of risdiplam-treated patients and more commonly than with placebo were fever, diarrhea, and headache. The most common serious AE in the risdiplam arm was pneumonia in 9 patients. There was a trend for more grade 3 to 4 AEs in the risdiplam group.
- Additional studies of risdiplam are ongoing (*Evrysdi AMCP Dossier 2020*). JEWELFISH is a Phase 2, open-label, exploratory study investigating the safety, pharmacokinetics, and pharmacodynamics of risdiplam in 174 patients 6

months to 60 years of age with SMA who had previously been treated with nusinersen, onasemnogene abeparvovec, or certain other investigational SMA therapies. RAINBOWFISH, which is currently enrolling patients, is a Phase 2, open-label study evaluating the use of risdiplam in pre-symptomatic SMA patients up to 6 weeks of age at the time of treatment initiation.

Other studies

- A recent observational cohort study showed benefit of nusinersen for adults aged 16 to 65 years with SMA. A clinically meaningful improvement (defined as an increase of 3 points or more in the HFMSE score compared to baseline) was observed with nusinersen treatment at 6 months in 35 of 124 patients (28%), at 10 months in 33 of 92 patients (36%), and at 14 months in 23 of 57 patients (40%) (*Hagenacker 2020*).
- A Cochrane review of 2 randomized controlled trials assessed the safety and efficacy of drug therapies (nusinersen and riluzole) designed to slow or stop the progression of SMA type 1. Riluzole is not indicated for the treatment of SMA. Authors concluded that intrathecal nusinersen probably prolongs ventilation-free and overall survival in infants with SMA type 1. Additionally, a greater proportion of infants treated with nusinersen achieved motor milestones. In the riluzole trial, 3 of 7 children treated with riluzole were still alive at the ages of 30, 48, and 64 months, whereas all 3 children in the placebo group died. None of the children in the riluzole or placebo group developed the ability to sit, which was the only milestone reported in the study (*Wadman et al 2019*).
- A Cochrane review of 14 randomized controlled trials evaluated the efficacy of various drug treatments, most of which are not indicated for the treatment of SMA, to slow the disease progression of SMA types 2 and 3. The trials evaluated gabapentin, hydroxyurea, nusinersen, olesoxime, phenylbutyrate, somatropin, thyrotropin-releasing hormone, valproic acid, and combination valproic acid/acetyl-L-cartinine. Treatment varied from 3 to 24 months. Overally, no treatment showed a clinically important effect on motor function in SMA types 2 or 3, except for intrathecal nusinersen, which showed a 3.7-point improvement in motor function in children with SMA type 2 based on the HFMSE scale with moderate quality evidence (*Wadman et al 2020*).

CLINICAL GUIDELINES

- **SMA Newborn Screening Working Group.** Treatment algorithm for infants diagnosed with SMA through newborn screening (*Glascock et al 2018*)
  - Clinical and preclinical data indicate that early treatment will be critical in order to modulate the rapid, progressive degeneration seen in SMA, particularly SMA type 1. Animal studies also show that the best results occur when drugs are given as early as possible.
  - Recommendations for the use of SMN-upregulating treatment for patients with a confirmed positive result for SMA on newborn screening are based on the number of *SMN2* copies, as follows:
    - 1 *SMN2* copy: probable SMA type 0. Treatment is recommended if the patient is truly pre-symptomatic. If symptoms are present, physician discretion is recommended. (Most patients with 1 copy of *SMN2* will be symptomatic at birth.)
    - 2 *SMN2* copies: probable SMA type 1. Treatment is recommended.
    - 3 *SMN2* copies: probable SMA type 2 or type 3. Treatment is recommended.
    - ≥ 4 *SMN2* copies: probable SMA type 3 or type 4. Waiting to treat is recommended; patients should be monitored and treated upon the onset of symptoms. (The committee was divided on this recommendation.)
  - In patients with ≥ 4 copies of *SMN2*, who are not immediately treated with a disease-modifying therapy for SMA, the following key recommendations are made:
    - Infants identified as having ≥ 4 *SMN2* copies should be referred to someone who can identify their exact copy number (some commercial laboratories report the result only as "≥ 4").
    - Routine follow-up care should ideally occur every 3 to 6 months until the patient reaches 2 years of age, and every 6 to 12 months thereafter. This would ensure the detection of very rare cases in which children with ≥ 4 *SMN2* copies have SMA type 1 or 2.
    - Certain follow-up assessments recommended include electromyography (EMG), compound muscle action potential (CMAP), myometry, physical examinations, and motor function scales.
  - The working group acknowledges that the future availability of new FDA-approved therapies will prompt the need for additional consideration by physicians and patients, as each drug will present unique benefits, risks, and burdens.

- **SMA Care Group**. Diagnosis and management of SMA. Part 1: recommendations for diagnosis, rehabilitation, orthopedic, and nutritional care (*Mercuri et al 2018[a])* and Part 2: pulmonary and acute care; medications, supplements, and immunizations; other organ systems; and ethics (*Finkel et al 2018*). The following recommendations outline aspects associated with supportive pharmacological care:
  - Over the last decade, the approach to treating the pulmonary manifestations of SMA has become more proactive, with introduction of therapies earlier in the disease process. Respiratory support should be the highest priority.
    - Management may include airway clearance, noninvasive positive pressure ventilation, and tracheotomy ventilation in select patients. Continuous positive airway pressure (CPAP) should not be used routinely.

- **European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy** *(Kirschner et al 2020*). With the recent approval of Zolgensma, many patients could be eligible for the gene therapy with the broadly defined approved indication. However, clinical trials studied very specific patient groups for gene therapy (eg, SMA type, age and weight), thus individual treatment decisions should be made on a case-by-case basis. The statement of 11 points highlights 3 areas including selection criteria, structural requirements for administration, and generation of additional evidence. Key points are as follows:
  - *Selection criteria*:
    - Traditional SMA types (0 to 4) alone are not enough to define patients who would most benefit from gene therapy. Age at onset, disease duration, and motor function status are key factors that predict response to treatment in symptomatic patients, whereas treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Although the approval of Zolgensma is based on clinical trials in patients ≤ 6 months old weighing less than 8.4 kg, it is indicated in patients up to 2 years old. However, little is known about the safety and efficacy in older and heavier patients; in these cases nusinersen is available as a treatment option. When administered after the age of 6 months and/or in advanced stages of the disease, caregivers should be made aware that there are no published data on efficacy and safety. It is important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.
    - In patients presenting with severe symptomatic disease, there is a high risk of living with severe disability despite the use of gene therapy. Palliative care is recommended as an alternative treatment option in these patients.
    - There is no evidence that combination therapy (eg, Zolgensma plus nusinersen) is superior to any single treatment alone. Before more evidence is available, combination of both approved therapies should not be part of routine care.
  - *Structural requirements for administration*: Providers performing gene therapy should have broad expertise in the assessment and treatment of SMA according to international standards. The ideal time between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive nature of the disease.
  - *Generation of additional evidence*: Data regarding safety and effectiveness should be collected for all treated patients. Institutions using Zolgensma should be adequately equipped with resources to safely administer the therapy and provide care and long-term monitoring. The statement suggests that patients weighing ≥ 13.5 kg may be best treated with Zolgensma in a clinical trial setting only.

SAFETY SUMMARY

- Contraindications
  - Evrysdi: none
  - Spinraza: none
  - Zolgensma: none
- Boxed Warning
  - Evrysdi: none
  - Spinraza: None
  - Zolgensma: acute serious liver injury, elevated amintransferases; higher risk in patients with pre-existing liver impairment
- Warnings and precautions
  - Evrysdi: none
  - Spinraza: thrombocytopenia, coagulation abnormalities, renal toxicity
  - Zolgensma: thrombocytopenia, elevated troponin

- AEs
  - Evrysdi:
    - Common AEs in infantile-onset SMA (≥ 10%): upper respiratory tract infection, pneumonia, constipation, vomiting, fever, diarrhea, and rash
    - Common AEs in later-onset SMA (≥ 10%): fever, diarrhea, and rash
  - Spinraza:
    - The most common AEs (≥ 20% of Spinraza-treated patients and occurred at least 5% more frequently vs placebo-treated patients) include:
      - Infantile-onset SMA: lower respiratory infection and constipation
      - Later-onset SMA: pyrexia, headache, vomiting, and back pain
  - Zolgensma
    - The most common AEs (≥ 5%) include: elevated aminotransferases and vomiting
- Use in specific populations:
  - Spinraza and Evrysdi, Pregnancy: may cause fetal harm (based on animal data).
  - Evrysdi, Hepatic impairment: Use should be avoided in patients with hepatic impairment.
  - Zolgensma, Pediatric use: Use in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evrysdi (risdiplam)	Powder for reconstitution (oral solution)	Oral	Once daily	Administer dose after a meal using the provided oral syringe.
Spinraza (nusinersen)	Injection	Intrathecal	4 loading doses: first 3 doses at 14-day intervals, 4th dose 30 days after the 3rd Maintenance dose every 4 months thereafter	To be given by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; administered as an intrathecal bolus over 1 to 3 minutes; sedation should be considered as indicated by the clinical condition of the patient; ultrasound or other imaging techniques should be considered to guide administration, particularly in younger patients.
Zolgensma (onasemnogene abeparvovec-xioi)	Injection	IV	One-time administration; 1.1 x 10^{14} vector genomes (vg)/kg	Administered over 60 minutes using a syringe pump. There are a total of 22 kit configurations, consisting of 2 to 9 vials (5.5 mL and/or 8.3 mL), to treat patients weighing 2.6 to 13.5 kg.

See the current prescribing information for full details

- Zolgensma: vials are shipped frozen and are stable under refrigeration for 14 days after receipt.

CONCLUSION

- SMA is a serious neuromuscular disease characterized by degeneration of motor neurons in the spinal cord and brainstem. Clinical features include progressive muscular atrophy and weakness.
  - SMA is caused by an inherited genetic mutation affecting the *SMN1* gene, causing a deficiency of the critical SMN protein.
  - Several subtypes of SMA exist, with varying severity and ages of onset.

- Zolgensma has the potential to significantly improve the disease course of SMA with a 1-time IV dose. Published efficacy data are limited to approximately 15 patients, all of whom had SMA type 1 and 2 copies of a modifying gene, *SMN2*.
  - Zolgensma is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein.
  - The main safety risks include elevated transaminases and potential acute serious liver injury.
- Nusinersen has demonstrated efficacy in patients with SMA types 1, 2, and 3 and in pre-symptomatic patients; however, nusinersen requires intrathecal dosing several times per year throughout the patient's lifetime.
- In pivotal trials, risdiplam improved motor function in people living with SMA over a large range of ages and levels of disease severity including types 1, 2, and 3.
  - Risdiplam helped infants survive longer without the need for permanent ventilation and sit without support for ≥ 5 seconds, a key motor milestone not normally seen in the natural course of the disease.
  - Risdiplam is an oral medication that is administered by the patient/caregiver, compared to intrathecal (nusinersen) and IV (Zolgensma) which require a healthcare professional.
- The specific place in therapy for each SMA agent, including the potential role for sequential treatment, requires further study.

APPENDIX

- **Bayley Scales of Infant and Toddler development Third Edition (BSID-III**) (*Evrydsi dossier 2020*)
  - BSID-III is intended for children age 1 to 42 months. The assessment is completed over 30 to 90 minutes and measures 5 developmental domains: adaptive behavior, cognition, language, motor, and social-emotional. Raw scores of each successfully completed item are converted to subtest scaled scores and to a composite standard score. The scores determine the child's performance compared with typically developing children of their age. While it is not a disease-specific measure, the BSID-III has high reliability and validity.
- **Hammersmith Functional Motor Scale – Expanded (HFMSE)** (*Spinraza dossier 2016*)
  - Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment.
  - Consists of 33 items evaluating the child's ability to perform activities. Each item is scored on a 3-point scale, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
  - The total score can range from 0 (all activities failed) to 66 (all activities achieved).
  - A clinically meaningful change has been estimated to be a 3-point change at 6 months.
- **Hammersmith Infant Neurological Examination (HINE)** (*De Sanctis 2016, Spinraza dossier 2016, FDA Medical Review 2016, Together in SMA 2016*)
  - Measures functional ability and achievement of motor milestones.
  - Contains 26 items; total possible score is 78. Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months. At 9 or 12 months, scores ≥ 73 are regarded as optimal.
    - Section 1 is based on the neurological exam (postures, cranial nerve function, reflexes, tone, and movements).
    - Section 2 (HINE-2) evaluates development of motor function based on 8 items (head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking); each item is scored between 0 and 2 to 4, for a maximum score of 26.
    - Section 3 evaluates the state of behavior (consciousness, social orientation, and emotional state).
- **Motor Function Measure 32 (MFM-32**) (*Evrydsi dossier 2020*)
  - MFM-32 is typically used in people older than 6 years; however it has been validated in children as young as 2 years old. The assessment typically takes around 30 to 40 minutes to complete. Each item of the MFM is scored using a 4-point Likert scale, ranging from 0 to 3, based on the subject's maximal abilities without assistance. The scores on each of the 32 items are summed and converted to a 0 to 100 total score; the lower the total score, the more severe the impairment.
- **Upper Limb Module (ULM)** (*Spinraza dossier 2016*)
  - Designed to assess upper limb functional abilities in patients with SMA, including young children and patients with severe contractures in the lower limbs.
  - Consists of 9 upper limb performance items that reflect activities of daily living.
  - The total score ranges from 0 to 18 points, with higher scores indicating greater functional abilities.
  - An increase of ≥ 2 points is considered clinically meaningful.

- A revised version of the ULM consists of 20 upper limb performance items.

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Publication Date: October 14, 2020

Prior Authorization Guideline

Guideline Name Viltepso (viltolarsen)

1 . Indications

Drug Name: Viltepso (viltolarsen)
Duchenne muscular dystrophy (DMD) Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 . Criteria

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

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting both of the following:

1.1 Diagnosis of Duchenne muscular dystrophy (DMD)

AND

1.2 Documentation of a confirmed mutation of the dystrophin gene amenable to exon 53 skipping

AND

2 - Patient is 4 years of age or older

AND

3 - Prescribed by or in consultation with a neurologist who has experience treating children

AND

4 - Dose will not exceed 80 milligrams per kilogram of body weight infused once weekly

AND

5 - Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is ambulatory, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA) [2, 3]

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

Approval Criteria

1 - One of the following:

1.1 All of the following:

1.1.1 Patient has been on therapy for less than 12 months

AND

1.1.2 Patient is tolerating therapy

AND

1.1.3 Dose will not exceed 80 milligrams per kilogram of body weight infused once weekly

AND

1.1.4 Prescribed by or in consultation with a neurologist who has experience treating children

AND

1.1.5 Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is maintaining ambulatory status, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA)

OR

1.2 All of the following:

1.2.1 Patient has been on therapy for 12 months or more

AND

1.2.2 Patient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients)

AND

1.2.3 Patient is tolerating therapy

AND

1.2.4 Dose will not exceed 80 milligrams per kilogram of body weight infused once weekly

AND

1.2.5 Prescribed by or in consultation with a neurologist who has experience treating children

AND

1.2.6 Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is maintaining ambulatory status, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA)

3 . References

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3. Per Clinical Consultation with a Pediatrician, April 25, 2019 and January 22, 2020.

Prior Authorization Guideline

Guideline Name Vyondys 53 (golodirsen)

1 . Indications

Drug Name: Vyondys 53 (golodirsen)
Duchenne muscular dystrophy (DMD) Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 . Criteria

Product Name: Vyondys 53	
Approval Length	6 Month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria	

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting both of the following:

1.1 Diagnosis of Duchenne muscular dystrophy (DMD)

AND

1.2 Documentation of a confirmed mutation of the dystrophin gene amenable to exon 53 skipping

AND

2 - Patient is 6 years of age or older [2, 3]

AND

3 - Prescribed by or in consultation with a neurologist who has experience treating children

AND

4 - Dose will not exceed 30 milligrams per kilogram of body weight infused once weekly

AND

5 - Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is ambulatory, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA) [2, 3]

Product Name: Vyondys 53	
Approval Length	12 Month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - One of the following:

1.1 All of the following:

1.1.1 Patient has been on therapy for less than 12 months

AND

1.1.2 Patient is tolerating therapy

AND

1.1.3 Dose will not exceed 30 milligrams per kilogram of body weight infused once weekly

AND

1.1.4 Prescribed by or in consultation with a neurologist who has experience treating children

AND

1.1.5 Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is maintaining ambulatory status, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA)

OR

1.2 All of the following:

1.2.1 Patient has been on therapy for 12 months or more

AND

1.2.2 Patient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients)

AND

1.2.3 Patient is tolerating therapy

AND

1.2.4 Dose will not exceed 30 milligrams per kilogram of body weight infused once weekly

AND

1.2.5 Prescribed by or in consultation with a neurologist who has experience treating children

AND

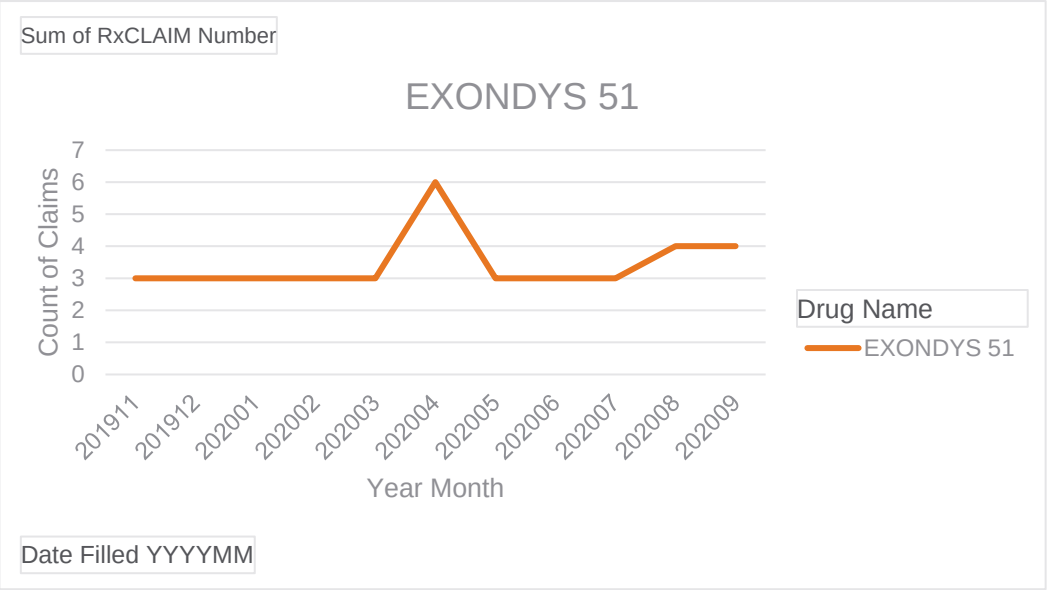
1.2.6 Submission of medical records (e.g., chart notes, laboratory values) documenting the patient is maintaining ambulatory status, as evaluated via the 6-minute walk test (6MWT) or North Star ambulatory assessment (NSAA)

3 . References

1. Vyondys 53 Prescribing Information. Sarepta Therapeutics, Inc. Cambridge, MA. December 2019.
2. Muntoni F, Frank DE, Morgan J, et al. Golodirsen induces exon skipping leading to sarcolemmal dystrophin expression in patients with genetic mutations amenable to exon 53 skipping [abstract]. Neuromuscul Disord. 2018;28:S5. Abstract D01.
3. Per Clinical Consultation with a Pediatrician, April 25, 2019 and January 22, 2020.

Nevada Medicaid
Muscular Dystrophy Agents
Fee for Service
October 1, 2019 – September 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
EXONDYS 51	2	38	1,064	2,224



RRR. Emflaza® (deflazacort)

Therapeutic Class: Emflaza® (deflazacort)
Last Reviewed by the DUR Board: October 19, 2017

Emflaza® (deflazacort) 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. Initial request:

1. The recipient must have a diagnosis of Duchenne muscular dystrophy (DMD); and

2. The recipient must be five years of age or older; and

3. The recipient must have received genetic testing for a mutation of the dystrophin gene, and one of the following:

a. Documentation of a confirmed mutation of the dystrophin gene; or

b. Muscle biopsy confirming an absence of dystrophin protein; and

4. The medication must be prescribed by or in consultation with a neurologist who has experience treating children; and

5. The recipient has had at least a three month trial and failure of prednisone (prednisolone or equivalent dose) or a documented intolerance to prednisone (prednisolone or equivalent dose) given at a dose of 0.75 mg/kg/day or 10 mg/kg/week; and

6. The dose will not exceed 0.9 milligrams per kilogram of body weight once daily.

2. Recertification request (the recipient must meet all of the following criteria):

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

a. Documentation of positive clinical response to Emflaza® therapy (e.g., improvement or preservation of muscle strength); and

b. The dose will not exceed 0.9 milligrams per kilogram of body weight once daily.

3. Prior Authorization Guidelines

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

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

MMM. Exondys 51® (eteplirsen)

Therapeutic Class:Exondys 51® (eteplirsen)
Last Reviewed by the DUR Board: August 24, 2017

Exondys 51® (eteplirsen) 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 of the following criteria are met and documented:

a. Initial request:

1. The recipient has a diagnosis of Duchenne muscular dystrophy (DMD); and

2. There is documentation of a confirmed mutation of the dystrophin gene amenable to exon 51 skipping; and

3. The medication is prescribed by or in consultation with a neurologist who has experience treating children; and

4. The prescribed dose does not exceed 30 milligrams per kilogram of body weight once weekly.

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

1. The recipient has been on therapy for less than 12 months; and

2. The recipient has experienced clinically significant benefit; and

3. The recipient is tolerating therapy; and

4. The prescribed dose will not exceed 30 milligrams per kilogram of body weight once weekly; and

5. The medication is prescribed by or in consultation with a neurologist who has experience treating children, or all of the following:

a. The recipient has been on therapy for 12 months or more; and

b. The recipient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients); and

c. The recipient has experienced clinically significant benefit; and

d. The recipient is tolerating therapy; and

e. The prescribed dose will not exceed 30 milligrams per kilogram of body weight once weekly; and

f. The medication is prescribed by or in consultation with a neurologist who has experience treating children.

2. Prior Authorization Guidelines

a. Prior authorization approvals will be for:

1. Initial request: six months.

2. Recertification request: one year.

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

Therapeutic Class Overview
Duchenne muscular dystrophy (DMD) Agents

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is 1 of 4 conditions known as dystrophinopathies, which are inherited, X-linked myopathic disorders due to a defect in the dystrophin gene that results in the primary pathologic process of muscle fiber degradation. The hallmark symptom is progressive weakness (*Darras 2018[a], Darras 2018[b], Muscular Dystrophy Association [MDA] 2019)*.
  - The other 3 conditions include: Becker muscular dystrophy (BMD), which is a mild form of DMD; an intermediate presentation between BMD and DMD; and DMD-associated dilated cardiomyopathy, which has little or no clinical skeletal or muscle disease (*MDA 2019*).
- DMD symptom onset is in early childhood, usually between the ages of 2 and 3 years old. The proximal muscles are affected first, followed by the distal limb muscles. Generally, the lower external muscles will be affected before the upper. The affected child may have difficulties jumping, walking, and running (*MDA 2019*).
- The prevalence of DMD ranges from 1 to 2 per 10,000 live male births; female-manifesting carriers are rarer, but can present with a range of symptoms that vary in their severities (*Birnkrant et al 2018, Darras 2018[a], Emflaza Food and Drug Administration [FDA] Medical Review 2017*).
- The clinical course and lifespan of patients with DMD is relatively short. Individuals are usually confined to a wheelchair by age 13, and many die in their late teens or twenties from respiratory insufficiency or cardiomyopathy. Although survival until adulthood is more common now, very few patients survive past the 3rd decade (*Darras 2018[a]*).
- Glucocorticoids (GCs) are the mainstay of therapy for DMD, including prednisone and deflazacort. Their beneficial effects include improving motor and pulmonary function, reducing the risk of scoliosis, delaying loss of ambulation (LoA), possible delay of cardiomyopathy progression, and improving overall survival (*Shieh et al 2018*).
  - Though not FDA-approved for DMD, prednisone is used off-label and considered a main drug of treatment.
- There are 3 FDA-approved agents for DMD which will be the focus of this overview: Emflaza (deflazacort), Exondys 51 (eteplirsen), and Vyondys 53 (golodirsen).
  - About 13% of patients with DMD carry the mutation for which eteplirsen is a potential therapy (*Birnkrant et al 2018).*
  - About 8% of patients with DMD carry the mutation for which golodirsen is a potential therapy (*Sarepta news release 2019[b]*).
- Three potential new therapies for DMD are in the emerging pipeline with ongoing Phase 3 trials.
  - Translarna (ataluren), an investigational new drug developed for DMD caused by nonsense mutations, was not approved by the FDA in October 2017. In a complete response letter (CLR) for the new drug application (NDA), the FDA requested additional evidence of effectiveness from well-controlled clinical trials. In February 2018, the FDA denied an appeal from the manufacturer and suggested that the currently enrolling Study-041 could serve as a confirmatory post-approval trial required in connection with the accelerated approval framework (*PTC Therapeutics news release 2017, PTC Therapeutics news release 2018).*
  - Golodirsen, developed for the treatment of DMD in patients with mutations amenable to exon 53 skipping, was also rejected by the FDA in August 2019. A CLR raised concerns over the risk of infections upon injection of the therapy and the possibility of toxicity to the kidneys. However, on December 12, 2019 the drug was granted accelerated approval in patients with confirmed mutation amenable to exon 53 skipping (*Sarepta news release 2019[a], Sarepta news release 2019[b]*).
  - Casimersen, developed to treat DMD in patients with mutations amenable to exon 45 skipping, is awaiting FDA review.
- Medispan Classes:
  - Endocrine and metabolic agents; corticosteroids; glucocorticosteroids
  - Neuromuscular agents; muscular dystrophy agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Emflaza (deflazacort)	-
Exondys 51 (eteplirsen)	-
Vyondys 53 (golodirsen)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Emflaza (deflazacort)	Exondys 51 (eteplirsen)*	Vyondys 53 (golodirsen)*
Treatment of DMD in patients 2 years of age and older	✔		
Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping		✔	
Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping			✔

*Accelerated approval was based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen and golodirsen. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

(*Prescribing information: Emflaza 2017, Exondys 51 2018, Vyondys 53 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

- There has been considerable experience using Emflaza (deflazacort) and other corticosteroids for the management of patients with DMD. A number of observational studies have been conducted to assess the long-term effects of corticosteroid use on muscle strength, the ability to walk, and on weight gain, among other outcomes. Overall, these studies concluded that patients taking steroids were significantly more functional and performed better on testing vs untreated patients and confirmed the prolongation of ambulation from a mean of 10.0 years in individuals treated with less than 1 year of corticosteroids to a mean of 11.2 years in individuals treated with daily prednisone and 13.9 years in individuals taking daily deflazacort (*Balaban et al 2005, Bello et al 2015, Kim et al 2015*).
- A Cochrane systematic review of 12 randomized controlled trials (RCTs) (N = 667) found that they provided moderate quality evidence for treatment with corticosteroids in patients with DMD. Compared to placebo, corticosteroids improved muscle strength and function (including respiratory muscle strength and function) for 6 months, with continued evidence of benefit at 1 year. There is no evidence other than from non-randomized trials to establish the effect of corticosteroids on prolongation of walking (*Matthews et al 2016*).
- The safety and efficacy of deflazacort for the treatment of DMD were demonstrated in 2 pivotal trials conducted in the 1980s and 1990s (*Angelini et al 1994, Emflaza Formulary Submission Dossier 2017, Griggs et al 2016)*.
  - A 52-week, Phase 3, double-blind (DB), placebo-controlled (PC), multi-center (MC), RCT (N = 196) was conducted to assess the safety and efficacy of deflazacort and prednisone vs placebo in boys aged 5 to 15 years old with DMD. For the first 12 weeks of the study (ie, Phase 1), patients were randomized to 1 of 4 groups (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, prednisone 0.75 mg/kg/day, or placebo). For the remainder of the study through week 52 (ie, Phase 2), patients initially randomized to placebo were re-randomized to 1 of the 3 active treatments (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, or prednisone 0.75 mg/kg/day). For the primary efficacy endpoint, all treatment groups demonstrated statistically significant improvements in muscle strength vs placebo from baseline to week 12. During Phase 2, only the deflazacort 0.9 mg/kg/day group maintained a statistically significant improvement in muscle strength vs prednisone-treated patients; however, both deflazacort groups outperformed the prednisone group by week 52 (secondary efficacy endpoint) (*Griggs et al 2016*).
    - In the opinion of the FDA, the results for the change from week 12 to week 52 were not interpretable. The larger increase in muscle strength score from week 12 to week 52 in the deflazacort 0.9 mg/kg/day group was mostly due to a lower score at week 12 in this group. Because the groups were not comparable at week 12, the comparisons of the treatment effect from weeks 12 to 52 were not considered meaningful (*Emflaza FDA Summary Review 2016).*

    - At week 52, patients taking prednisone had significantly more weight gain than both deflazacort groups. The most frequent adverse effects (AEs) reported were: Cushingoid appearance, erythema, hirsutism, increased weight, headache, and nasopharyngitis.
  - A 2-year, Phase 3, DB, PC, MC, RCT (N = 29) was conducted to evaluate the change in muscle strength from baseline to 2 years or LoA, whichever occurred first, in boys aged 5 to 11 years old with DMD and symptom onset before age 5. By year 2, the study failed to show a statistically significant result for change in muscle strength, possibly because of a limited number of patients remaining in the placebo arm (12 patients vs 3 patients). The median time to LoA was statistically significant for deflazacort vs placebo (63.0 months [95% CI: 35.1 to not estimable] vs 31.9 months [95% CI: 13.6 to 54.6], p = 0.0052) (*Angelini et al 1994*).
- Exondys 51 (eteplirsen) was evaluated in 3 clinical studies in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
  - Study 201 was a 24-week, Phase 2b, DB, PC, RCT (N = 12) that evaluated eteplirsen's ability to induce dystrophin production (surrogate endpoint) and improve distance walked on the 6-minute walk test (6MWT, clinical outcome) in boys aged 7 to 13 years old that were stable on corticosteroid treatment for at least 6 months. Patients were randomized to weekly intravenous (IV) infusions of 30 or 50 mg/kg/wk eteplirsen or placebo for 24 weeks (n = 4/group). Placebo patients switched to 30 or 50 mg/kg eteplirsen (n = 2/group) at week 25. Study 202 was a 212-week, ongoing Phase 2, open-label (OL), MC extension study; all 12 patients who participated in Study 201 continued treatment in Study 202 (*Mendell et al 2013*).
    - The Study 201 authors concluded that at week 24, dystrophin-positive fibers increased by 23% from baseline in patients treated with 30 mg/kg eteplirsen, with no significant increases in the placebo group (p ≤ 0.002). Greater increases continued to occur by week 48 (52% and 43% in the 30 and 50 mg/kg groups, respectively). The authors also concluded that 6 ambulation-evaluable patients taking eteplirsen demonstrated an increase in the 6MWT (67.3 m, p ≤ 0.001) vs placebo.
    - The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the normal dystrophin level in healthy subjects (*Exondys 51 prescribing information 2018*).
      - The FDA noted that for the week 180 analysis, archived pre-treatment muscle biopsy samples were available for re-analysis from only 3 patients in Studies 201/202, and samples from controls were also obtained from different muscle groups than the eteplirsen-treated patients; therefore, the true change in dystrophin was difficult to estimate (*Exondys 51 FDA Summary Review 2016).*
      - In contrast to the conclusions of Mendell et al, the FDA found no significant difference in the change in 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Additionally, Study 202 failed to provide evidence of a clinical benefit when compared to the external control group (primary endpoint, week 48) (*Exondys 51 FDA Summary Review 2016).*
  - A confirmatory Phase 3, 144-week, OL, MC study (PROMOVI) was conducted in 109 ambulatory males between ages 7 to 16 years old on a stable dose of corticosteroids for at least 24 weeks. Patients in the treated group (DMD amenable to exon 51 skipping) received once weekly IV infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks). Patients in the untreated group did not receive treatment. The primary outcome was change in 6MWT distance from baseline to 96 weeks (*Alfano et al 2019*).
    - Results at 48 weeks (N = 13) showed a median increase in dystrophin levels from 0.16% at baseline to 0.44% (p < 0.05). The median increase after 48 weeks was 0.1%. The study completed in 2019, and full results are pending.
  - Vyondys 53 (golodirsen) was granted accelerated approval based on a 2-part clinical study (*FDA news release 2019, Sarepta news release 2019[b], Vyondys 53 prescribing information 2019*).
    - Part 1 was a DB, PC, dose-titration study (N = 12). Patients were randomized 2:1; 8 patients received 4 escalating dose levels of golodirsen IV (ranging from 4 mg/kg/week to 30 mg/kg/week) for 2 weeks at each level, while 4 patients received placebo.
    - Part 2 was an OL study that included the 12 patients from Part 1, plus 13 additional treatment-naïve patients with DMD amenable to exon 53 skipping. Patients were given golodirsen at a dose of 30 mg/kg/week. Results showed that dystrophin levels increased (on average) from 0.10% of normal at baseline to 1.02% of normal after 48 weeks of treatment (mean change in dystrophin of 0.92% of normal levels, p < 0.001).
    - This study only evaluated a surrogate endpoint; a clinical benefit of golodirsen was not established. An ongoing, confirmatory Phase 3 trial (ESSENCE) is currently being conducted to assess whether golodirsen improves motor function in patients with DMD amenable to exon 53 skipping.

CLINICAL GUIDELINES

- DMD Care Considerations Working Group: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management *(Birnkrant et al 2018).*
  - Physiotherapy and treatment with GCs is the mainstay of DMD treatment and should continue after LoA. The benefits of long-term GC therapy have been shown to include LoA at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.
  - Recent studies confirm the benefits of starting GCs in younger children, and the consensus is to begin steroid regimens before significant physical decline. Recommended starting doses include prednisone or prednisolone 0.75 mg/kg/day, or deflazacort 0.9 mg/kg/day. Patients should be reassessed at regular intervals to monitor functional decline and consider therapy updates.
- American Academy of Neurology (AAN) Practice guideline update summary: Corticosteroid treatment of DMD (*Gloss et al 2016*).
  - The ideal time to start and stop therapy is not currently known.
  - In children with DMD, prednisone should be offered for improving strength and pulmonary function.
  - Prednisone may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age.
  - Deflazacort may be offered for improving strength and timed motor function and delaying age at LoA by 1.4 to 2.5 years.
  - Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5 to 15 years of follow-up.
  - Deflazacort and prednisone may be equivalent in improving motor function.
  - Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort.
  - Deflazacort may be associated with a greater risk of cataracts than prednisone.
  - The preferred dosing regimen of prednisone is 0.75 mg/kg/day. Over 12 months, prednisone 10 mg/kg/weekend is equally effective, with no long-term data available. Prednisone 0.75 mg/kg/day is associated with significant risk of weight gain, hirsutism, and Cushingoid appearance.
  - Calcium and vitamin D intake are optimized and encouraged in clinical practice, as these children have several risk factors for low bone density and fractures, such as chronic corticosteroid use and decreased weight-bearing activities.
    - The American College of Rheumatology Task Force osteoporosis guideline recommends calcium and vitamin D supplementation for patients taking corticosteroids (any dose with an anticipated duration of ≥ 3 months) in order to maintain a total calcium intake of 1200 mg/day and vitamin D intake of 800 IU/day through dietary sources, supplementation, or both.

SAFETY SUMMARY

Emflaza (deflazacort)

- Contraindications
  - Hypersensitivity to deflazacort or to any components of the formulation: Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.
- Warnings and precautions of deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi's sarcoma, risk of serious AEs in infants because of the benzyl alcohol preservative, thromboembolic events, and anaphylaxis.
  - The most common AEs (≥ 10% and greater than placebo) with deflazacort use were Cushingoid appearance (33% with deflazacort vs 12% with placebo), increased weight (20% vs 6%), increased appetite (14% vs 2%), upper respiratory tract infection (12% vs 10%), cough (12% vs 6%), pollakiuria (12% vs 2%), hirsutism (10% vs 2%), central obesity (10% vs 4%), and nasopharyngitis (10% vs 6%).

Exondys 51 (eteplirsen)

- No contraindications known at this time.
- Warnings/precautions:

- Hypersensitivity reactions: Reactions including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension have occurred in patients. If hypersensitivity reactions occur, appropriate medical treatment should be instituted, and slowing of the infusion or interruption of eteplirsen therapy should be considered.

- The most common AEs (incidence ≥ 35% and higher than placebo) were balance disorder and vomiting.

Vyondys 53 (golodirsen)

- No contraindications known at this time.
- Warnings/precautions:
  - Hypersensitivity reactions: Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation, have occurred in patients receiving golodirsen. If a hypersensitivity reaction occurs, appropriate medical treatment should be instituted and slowing of the infusion or interruption of golodirsen therapy should be considered.
  - Renal toxicity: Based on animal data, golodirsen may cause renal toxicity. Renal function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients.
- The most common AEs (incidence ≥ 20% and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Emflaza (deflazacort)	Tablets, suspension	Oral	Daily	May be taken with or without food. No dosage adjustment in renal impairment. No dosage adjustment in mild and moderate hepatic impairment; has not been studied in severe hepatic impairment
Exondys 51 (eteplirsen)	Injection	IV	Once weekly	Administer IV infusion over 35 to 60 minutes If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting therapy.
Vyondys 53 (golodirsen)	Injection	IV	Once weekly	Administer IV infusion over 35 to 60 minutes If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting therapy.

See the current prescribing information for full detail

CONCLUSION

- GCs remain the mainstay of therapy for DMD, and are currently recommended for all patients. The benefits of long-term GC therapy have been shown to include LoA at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery *(Birnkrant et al 2018*).
- Emflaza (deflazacort) tablets and oral suspension are indicated for the treatment of DMD in patient's ≥ 5 years of age.
- The efficacy and safety of deflazacort were demonstrated in 2 pivotal DB, PC, MC, RCTs conducted in the 1980s and 1990s. Results showed that daily use of either deflazacort or prednisone was effective in preserving muscle strength over a 12-week period (*Griggs et al 2016).*

- Exondys 51 (eteplirsen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping; this includes only about 13% of the overall patient population. Similarly, Vyondys 53 (golodirsen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping; this includes only about 8% of the overall patient population.
  - These indications were approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen or golodirsen.
  - Continued approval for these indications may be contingent upon verification of a clinical benefit in confirmatory trials (ie, PROMOVI, ESSENCE). Methodological flaws in the study designs etepliren were brought to light during the FDA review process and have called into question whether the production of dystrophin is high enough to provide a true clinical benefit for patients with DMD.

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Publication Date: January 6, 2020

Prior Authorization Guideline

Guideline Name Qutenza (capsaicin)

1 . Indications

Drug Name: Qutenza (capsaicin)
Neuropathic pain Indicated for the management of neuropathic pain associated with postherpetic neuralgia.

2 . Criteria

Product Name: Qutenza	
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of neuropathic pain associated with postherpetic neuralgia	

AND

2 - History of failure or intolerance to over-the-counter capsaicin

Product Name: Qutenza	
Approval Length	3 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - It has been at least 3 months since the last Qutenza application/administration [A]

AND

2 - Patient experienced pain relief with a prior course of Qutenza

AND

3 - Patient is experiencing a return of neuropathic pain

3 . Endnotes

A. Treatment with capsaicin may be repeated every three months as warranted by the return of pain (but not more frequently than every three months). [1]

4 . References

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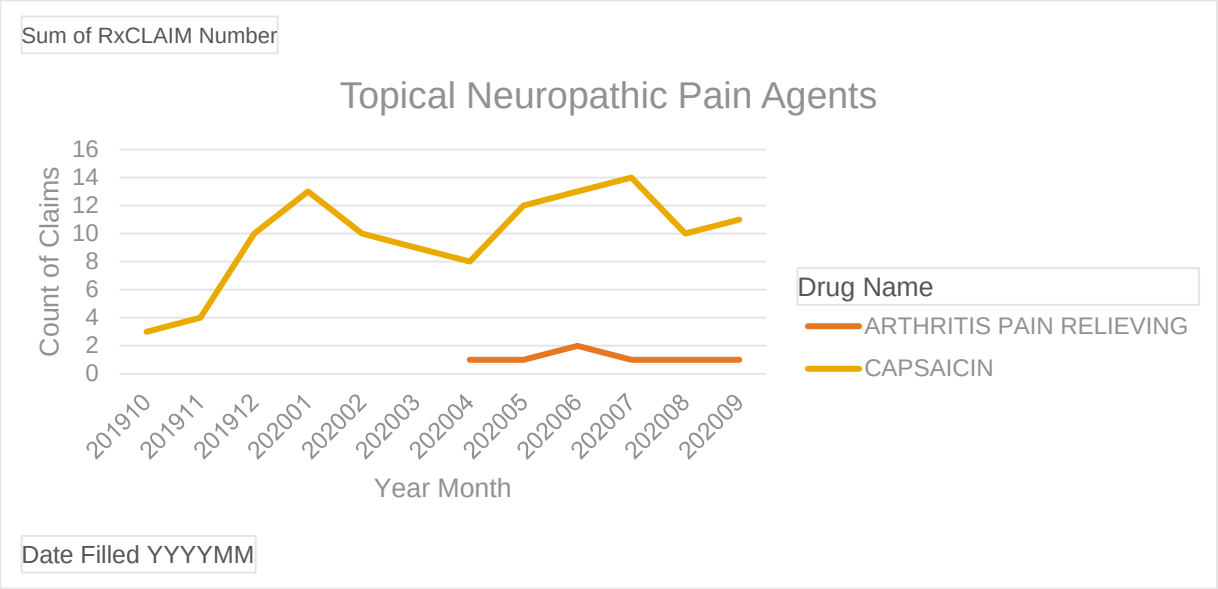
Nevada Medicaid
Topical Neuropathic Pain Agents
Fee for Service
October 1, 2019 – September 30, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
ARTHRITIS PAIN RELIEVING	7	7	197	399
CAPSAICIN	56	117	2,789	10,980



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 2019*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2018*).
- 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 2020, Gralise 2020, Horizant 2016, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2019, Qutenza 2020, 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 2020[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 2020[b]*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2020[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 2020[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 2020[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 2020[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 U.S. population is estimated to be 2% to 3% and increases with age *(Goldenberg 2019)*. 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 2019*).
- 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 2019*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2019*). 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 2019*).

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 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 1 month of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia in adults	✔				✔					✔
Management of fibromyalgia in adults and pediatric patients 13 years of age and older	✔									
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; pain that is mild or not expected to persist for an extended period of time; acute pain; or 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 2020, Gralise 2020, Horizant 2020, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2019, Qutenza 2020, 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 (BPI), 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 (*Tanenberg et 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 (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by BPI Modified Short Form (BPI-MSF) average pain (*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, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, 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 compared to placebo, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score (*Lyrica prescribing information 2019*, *Siddall et al 2006, Vranken et al 2008*).
- The efficacy of capsaicin 8% in diabetic peripheral neuropathy was assessed in a placebo-controlled trial *(Simpson et al 2016)*. The primary endpoint, percentage reduction in average daily pain score from baseline through 8 weeks, was significantly improved with capsaicin 8%. Patients treated with capsaicin also had significant improvements in median time to treatment response and in sleep interference scores through week 8.

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 ≥ 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 occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each 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 et al 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*).
  - Duloxetine is approved for treatment of fibromyalgia in patients age 13 years and older. Pediatric approval was supported by findings of a 13-week, placebo-controlled RCT (N = 184) of patients age 13 to 17 years with juvenile fibromyalgia *(Upadhyaya et al 2019)*. The primary outcome, mean change in BPI average pain severity, was not statistically different between groups; however, significantly more duloxetine- vs placebo-treated patients had a treatment response of ≥ 30% reduction (52% vs 36%) and ≥ 50% reduction (40% vs 24%) on BPI average pain severity.

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 adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 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 ≥ 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 ≥ 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 support 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 2020*). 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 [update in progress 2020], 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.
  - 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 2020 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 2020*).
  - 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

- 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

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- 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.

- Duloxetine may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- 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.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- Tapentadol ER should not be abruptly discontinued in patients who may be physically dependent on opioids. Rapid discontinuation in these patients may result in withdrawal symptoms, uncontrolled pain, and suicide. Mixed agonist/antagonist or partial agonist analgesics should not be used concomitantly with tapentadol ER.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Gabapentin, gabapentin enacarbil, pregabalin, and pregabalin ER carry warnings regarding the risk of respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment.
- 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.
- Topical capsaicin carries warnings for severe irritation with unintended exposure, pain associated with application, and temporary reductions in sensory function.
- The following monitoring parameters are recommended with treatment:
  - 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.
  - 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, 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.
  - Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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
Qutenza (capsaicin)	Patch	Transdermal	30-minute (DPN) or 60-minute (PHN) 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; DPN = diabetic peripheral neuropathy; ESRD = end-stage renal impairment; PHN = postherpetic neuralgia
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 and capsaicin 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 2020[b], Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, capsaicin, 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 2019*).
  - 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*).

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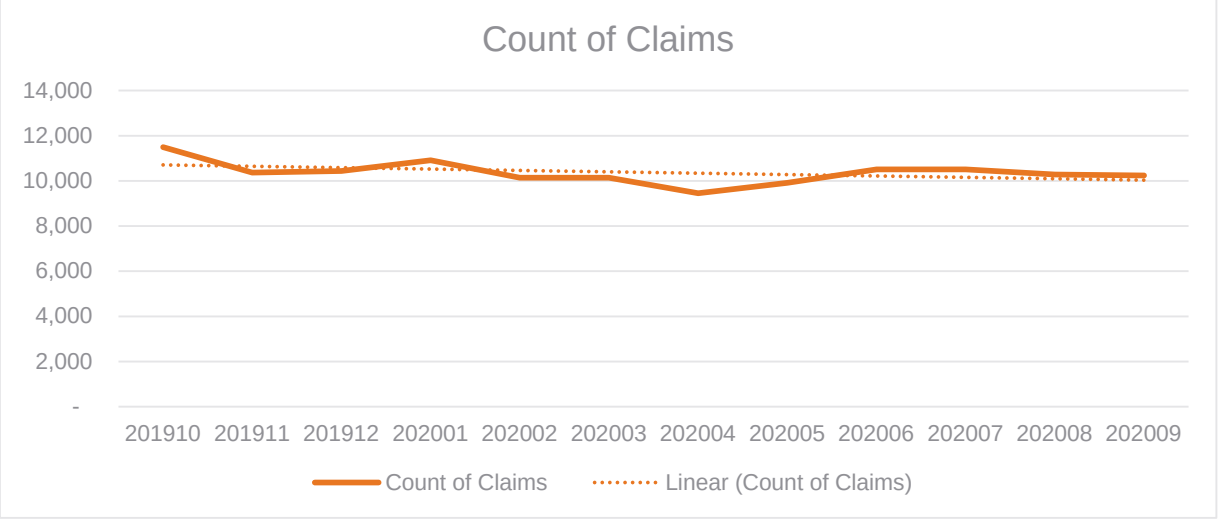
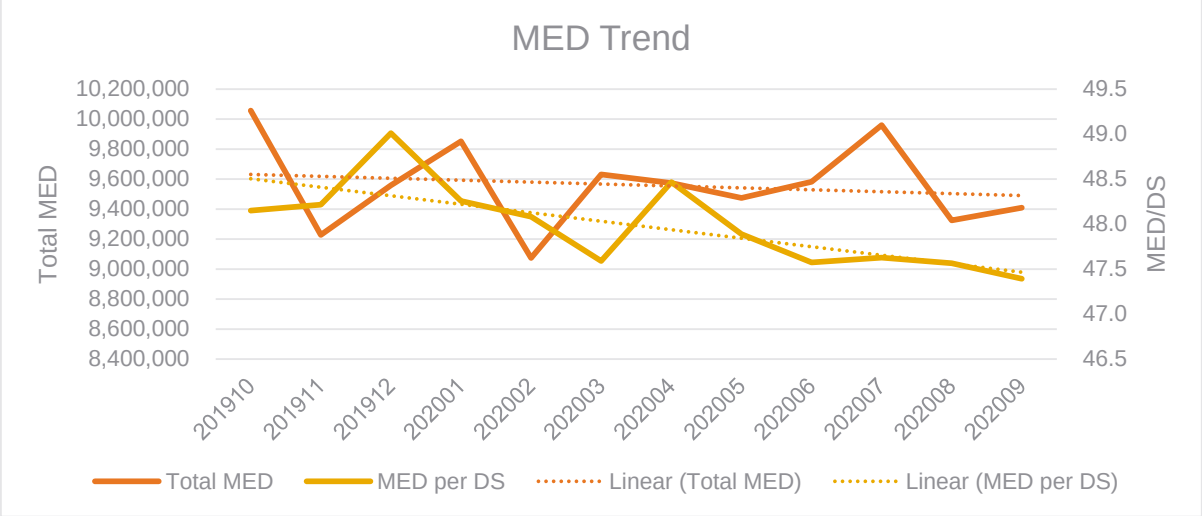
Board Requested Reports

Nevada Medicaid

Opioid Trends
Fee for Service
October 1, 2019 - September 30, 2020

Date Filled	Count of Claims	Total MED	Days Supply	Count of Members	Total Qty	MED per DS
201910	11,494	10,056,953	208,870	9,846	701,344	48.1
201911	10,367	9,228,183	191,391	9,105	642,903	48.2
201912	10,440	9,558,807	195,030	9,054	660,141	49.0
202001	10,910	9,852,477	204,167	9,433	690,568	48.3
202002	10,141	9,075,013	188,735	9,001	632,687	48.1
202003	10,143	9,631,393	202,379	8,773	681,087	47.6
202004	9,454	9,573,572	197,532	8,242	660,493	48.5
202005	9,915	9,474,878	197,849	8,636	660,480	47.9
202006	10,508	9,582,580	201,426	9,070	676,160	47.6
202007	10,511	9,960,098	209,128	9,028	703,515	47.6
202008	10,281	9,324,704	196,043	9,015	659,854	47.6
202009	10,237	9,409,372	198,539	8,992	672,065	47.4





Nevada Medicaid

Opioid Trends - Top Ten Members
Fee for Service
July 1, 2020 - September 30, 2020

Member ID Encrypted	Count of Claims	Days Supply	Total Quantity	Total MED
11110100737	12	340	2,040	69,600
77771952964	8	240	1,050	67,500
33330458115	7	210	1,320	64,800
49044066667	8	214	1,232	60,480
22222296971	6	165	660	59,400
44446597311	6	180	585	56,700
99990949361	7	159	1,124	51,480
11117226669	11	257	1,172	51,300
94483233334	7	210	720	48,600
44448546720	6	180	1,260	47,250
66667788323	10	300	1,080	47,250

Nevada Medicaid

Opioid Trends - Top Ten Members Detail

Fee for Service

July 1, 2020 - September 30, 2020

Member ID Encrypted	Generic Drug Name	Count of Claims	Days Supply	Total Qty
11110100737	METHADONE HCL TAB 10 MG	4	112	1080
11110100737	MORPHINE SULF TAB CR 100 MG	4	112	480
11110100737	OXYCODONE HCL TAB 30 MG	4	116	480
11117226669	MORPHINE SULF TAB CR 15 MG	2	60	180
11117226669	MORPHINE SULF TAB CR 60 MG	3	90	270
11117226669	MORPHINE SULFATE IV SOLN PF 10 MG/ML	2	2	2
11117226669	OXYCODONE HCL TAB 30 MG	4	105	720
22222296971	FENTANYL TD PAT 72H 75MCG/HR	3	90	60
22222296971	OXYCODONE HCL TAB 30 MG	3	75	600
33330458115	MORPHINE SULF TAB CR 100 MG	3	90	360
33330458115	OXYCODONE HCL TAB 20 MG	4	120	960
44446597311	FENTANYL TD PAT 72H 100MCG/HR	3	90	45
44446597311	OXYCODONE HCL TAB 30 MG	3	90	540
44448546720	HYDROCODONE-APAP TAB 10-325 MG	3	90	270
44448546720	OXYCODONE HCL TAB 30 MG	3	90	990
49044066667	MORPHINE SULF TAB CR 60 MG	4	112	336
49044066667	OXYCODONE HCL TAB 30 MG	4	102	896
66667788323	MORPHINE SULF TAB CR 30 MG	4	120	360
66667788323	MORPHINE SULF TAB CR 60 MG	3	90	270
66667788323	OXYCODONE HCL TAB 30 MG	3	90	450
77771952964	FENTANYL TD PAT 72H 100MCG/HR	2	60	60
77771952964	METHADONE HCL TAB 10 MG	3	90	450
77771952964	OXYCODONE HCL TAB 30 MG	3	90	540
94483233334	OXYCOD TAB ER12H DETER 80MG	4	120	360
94483233334	OXYCODONE W/ APAP TAB 10-325MG	3	90	360
99990949361	OXYCOD TAB ER12H DETER 40MG	1	30	60
99990949361	OXYCODONE HCL TAB 30 MG	6	129	1064

Nevada Medicaid

Fee for Service - Opioid Trends - Top Ten Prescribers

By Morphine Equivalent Dose (MED)

Quarter Filled	Prescriber	City	Degree	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2020 Q3	C	RENO	DO	- Anesthesiology	138	374	11,373	46,445	628,366	55	0.40
2020 Q3	W	SPARKS	MD	- Anesthesiology	108	264	7,753	22,268	536,382	69	0.64
2020 Q3	E	LAS VEGAS	PAC	- Orthopedic surgery	176	375	10,816	34,987	513,172	47	0.27
2020 Q3	B	LAS VEGAS	PAC	- Physician Assistant	88	229	6,487	21,743	501,870	77	0.88
2020 Q3	M	LAS VEGAS	PAC	- Physician Assistant	145	371	10,942	37,051	492,020	45	0.31
2020 Q3	BB	LAS VEGAS	MD	- Anesthesiology	134	282	7,738	26,210	442,113	57	0.43
2020 Q3	AA	LAS VEGAS	MD	- Hospitalist	97	203	5,541	17,911	433,129	78	0.81
2020 Q3	G	HENDERSON	PAC	- Physician Assistant	45	100	2,920	10,875	431,775	148	3.29
2020 Q3	I	LAS VEGAS	NP	- Acute Care	139	289	7,567	26,214	430,986	57	0.41
2020 Q3	FF	LAS VEGAS	NP	- Pain Management	105	247	7,263	22,515	414,693	57	0.54
2020 Q2	C	RENO	DO	- Anesthesiology	155	409	12,323	51,467	671,128	54	0.35
2020 Q2	W	SPARKS	MD	- Anesthesiology	100	252	7,441	21,343	542,368	73	0.73
2020 Q2	E	LAS VEGAS	PAC	- Orthopedic surgery	173	365	10,816	35,909	525,503	49	0.28
2020 Q2	B	LAS VEGAS	PAC	- Physician Assistant	84	230	6,570	22,012	480,426	73	0.87
2020 Q2	BB	LAS VEGAS	MD	- Anesthesiology	138	318	8,672	27,796	469,801	54	0.39
2020 Q2	FF	LAS VEGAS	NP	- Pain Management	119	243	7,195	21,609	426,363	59	0.50
2020 Q2	G	HENDERSON	PAC	- Physician Assistant	38	92	2,665	10,140	416,700	156	4.11
2020 Q2	M	LAS VEGAS	PAC	- Physician Assistant	136	319	9,243	31,204	415,883	45	0.33
2020 Q2	Y	HENDERSON	MS	- Nurse Practitioner	85	171	4,582	15,750	376,881	82	0.97
2020 Q2	O	HENDERSON	PAC	- Physician Assistant	73	194	5,819	20,460	366,330	63	0.86

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

Quarter Filled	Prescriber	City	Degree	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2020 Q3	V	RENO	MD	- Radiology	1	2	24	240	3,600	150	150.00
2020 Q3	L	LAS VEGAS	MD	- Specialist	2	6	180	1,110	49,950	278	138.75
2020 Q3	H	LAS VEGAS	DO	- Hospitalist	1	2	60	180	8,100	135	135.00
2020 Q3	Z	CARSON CITY	MD	- Family Medicine	1	1	14	42	1,890	135	135.00
2020 Q3	N	EAST MEADOW	-	- Student Program	1	1	3	18	405	135	135.00
2020 Q3	EE	CARSON CITY	MD	- Radiology	1	1	14	120	1,800	129	128.57
2020 Q3	Q	PAHRUMP	MD	- Internal Medicine	1	3	90	360	10,800	120	120.00
2020 Q3	A	RENO	APN	- Registered Nurse	1	1	30	10	3,600	120	120.00
2020 Q3	CC	MINNEAPOLIS	MSN	- Nurse Practitioner	1	1	30	120	3,600	120	120.00
2020 Q3	T	LAS VEGAS	DO	- Internal Medicine	2	6	180	1,080	40,500	225	112.50
2020 Q2	S	LAS VEGAS	PAC	- Physician Assistant	1	1	5	30	1,350	270	270.00
2020 Q2	P	SAN DIEGO	MD	- Anesthesiology	1	1	30	150	6,750	225	225.00
2020 Q2	DD	CARSON CITY	MD	- Family Medicine	1	3	90	360	16,200	180	180.00
2020 Q2	F	LAS VEGAS	DO	- Family Medicine	1	1	30	120	5,400	180	180.00
2020 Q2	D	SALT LAKE CITY	MD	- Student Program	1	1	15	5	2,700	180	180.00
2020 Q2	X	IONIA	PAC	- Physician Assistant	1	1	15	5	2,700	180	180.00
2020 Q2	J	SALT LAKE CITY	DNP	- Acute Care	1	1	4	40	600	150	150.00
2020 Q2	L	LAS VEGAS	MD	- Specialist	2	6	180	1,110	49,950	278	138.75
2020 Q2	GG	SALT LAKE CITY	MD	- Anesthesiology	2	3	60	195	16,200	270	135.00
2020 Q2	U	LAS VEGAS	DO	- Internal Medicine	1	2	60	180	8,100	135	135.00

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

April 1, 2020 – September 30, 2020

Top 10 Classes by Claim Count

2020 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,354	$ 2,718,576.48
SYMPATHOMIMETICS	18,204	$ 2,750,474.96
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,434	$ 212,309.13
OPIOID COMBINATIONS	15,356	$ 435,212.10
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	13,495	$ 283,852.08
CENTRAL MUSCLE RELAXANTS	13,072	$ 221,955.87
HMG COA REDUCTASE INHIBITORS	11,119	$ 383,497.02
DIBENZAPINES	10,195	$ 396,108.69
OPIOID AGONISTS	10,013	$ 492,872.44
ANTIANXIETY AGENTS - MISC.	9,420	$ 144,132.74

2020 Q2

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	26,970	$ 2,586,195.85
SYMPATHOMIMETICS	18,081	$ 2,680,147.74
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,136	$ 207,566.67
OPIOID COMBINATIONS	15,057	$ 418,280.01
CENTRAL MUSCLE RELAXANTS	12,685	$ 217,160.24
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	12,494	$ 289,753.33
HMG COA REDUCTASE INHIBITORS	10,777	$ 342,384.03
DIBENZAPINES	10,020	$ 350,038.85
OPIOID AGONISTS	9,824	$ 556,462.19
ANTIANXIETY AGENTS - MISC.	9,187	$ 142,157.53

Top 10 Classes by Amount Paid

2020 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	114	$ 13,239,554.37
ANTIRETROVIRALS	1,842	$ 4,035,866.49
INSULIN	4,776	$ 3,242,194.85
SYMPATHOMIMETICS	18,204	$ 2,750,474.96
ANTICONVULSANTS - MISC	27,354	$ 2,718,576.48
BENZISOXAZOLES	5,967	$ 2,690,060.59
ANTIPSYCHOTICS - MISC	2,995	$ 2,675,174.38
ANTINEOPLASTIC ENZYME INHIBITORS	203	$ 2,447,970.60
LOCAL ANESTHETICS - TOPICAL	1,903	$ 2,282,463.41
CYSTIC FIBROSIS AGENTS	232	$ 2,175,569.35

2020 Q2

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	105	$ 13,082,576.52
ANTIRETROVIRALS	1,824	$ 3,970,933.07
INSULIN	4,831	$ 3,389,177.21
LOCAL ANESTHETICS - TOPICAL	1,999	$ 3,104,137.04
SYMPATHOMIMETICS	18,081	$ 2,680,147.74
ANTIPSYCHOTICS - MISC.	3,046	$ 2,614,342.87
ANTICONVULSANTS - MISC.	26,970	$ 2,586,195.85
BENZISOXAZOLES	5,886	$ 2,566,923.80
ANTINEOPLASTIC ENZYME INHIBITORS	178	$ 2,088,167.72
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	294	$ 2,085,013.78

cDUR Quarterly Report

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

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	632,907	146,186	23.1%
Rejected	502,318	175,356	34.9%
Reversed	102,053	32,270	31.6%
Total	***1,237,278***	***353,812***	***28.6%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
45,537	**$17,608,663**	**24,395**	**$8,735,354**	**69,932**	**$26,344,016**	**160,017**	**$64,696,867**

cDUR Detailed Activity Summary:

Intervention Type	Total	Paid Rxs		Rejected Rxs		Reversed Rxs	
	Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions
Dosing/Duration (DOSECHEK)	44,634	35,676	79.9%	1,108	2.5%	7,850	17.6%
Drug-Drug Interaction (DDI-DTMS)	125,453	57,060	45.5%	60,247	48.0%	8,146	6.5%
Duplicate Therapy (DUPTHER)	100,435	44,006	43.8%	48,074	47.9%	8,355	8.3%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	18	11	61.1%	N/A	N/A	7	38.9%
Duplicate Rx (DUPRX)	82,804	9,422	11.4%	65,490	79.1%	7,892	9.5%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	18	5	27.8%	N/A	N/A	13	72.2%
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	13	6	46.2%	N/A	N/A	7	53.8%
Refill Too Soon	437	N/A	N/A	437	100.0%	N/A	N/A
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***353,812***	***146,186***	***41.3%***	***175,356***	***49.6%***	***32,270***	***9.1%***

cDUR Detailed Saving Outcomes Summary:

Intervention Type	Current		Accruing		Total		Total Year to Date	
	Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
Dosing/Duration (DOSECHEK)	1,167	$2,182,920	1,822	$3,398,246	2,989	$5,581,166	6,124	$24,606,130
Drug-Drug Interaction (DDI-DTMS)	4,250	$309,133	4,483	$916,776	8,733	$1,225,908	18,065	$4,040,350
Duplicate Therapy (DUPTHER)	5,016	$1,571,721	9,343	$3,326,634	14,359	$4,898,356	24,030	$13,388,432
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	0	$0	0	$0	0	$0	3	$14
Duplicate Rx (DUPRX)	34,707	$13,500,523	8,660	$1,087,156	43,367	$14,587,679	109,766	$22,443,420
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	8	$111	38	$1,182	46	$1,293	45	$1,802
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	2	$759	0	$0	2	$759	16	$3,313
Refill Too Soon	387	$43,496	49	$5,359	436	$48,855	1,968	$213,406
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***45,537***	***$17,608,663***	***24,395***	***$8,735,354***	***69,932***	***$26,344,016***	***160,017***	***$64,696,867***

Claims Summary:

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

cDUR Savings Outcomes Summary:

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

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

Nevada Medicaid

RetroDUR

Fee for Service

Third Quarter 2020

Q3 2020

Type	Sent	Responses	Prescribers	Recipients	Response Rate
Support Act - Opiods and Antipsychotics	98	7	75	98	7.14%
Support Act - Opiod and Benzodiazepine	111	15	81	111	13.51%
Cont. Glucose Monitors	119	29	43	119	24.37%