Nevada Medicaid Drug Use Review Board Meeting

July 22, 2021

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Steve Sisolak
Governor

Richard Whitley, MS
Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DIVISION OF HEALTH CARE FINANCING AND POLICY

Helping people. It's who we are and what we do.

Suzanne Bierman, JD MPH
Administrator

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting: June 1, 2021
Date of Revision: June 4, 2021

Date of Meeting: July 22, 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).

Remote Meeting Access: Microsoft Teams

OR

http://bit.ly/34jyAN2

The physical location for this meeting which is open to the public is at:

Surestay Plus Hotel by Best Western Reno Airport
1981 Terminal Way
Reno, NV 89502
(775) 348-6370

Space is limited at the physical location and subject to any applicable social distancing or mask wearing requirements as may be in effect at the time of the meeting for the county in which the physical meeting is held.

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 rxinfo@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: Phone: (952) 222-7450
Event: 403 932 643#

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

YOU MAY BE UNMUTED BY THE HOST WHEN SEEKING PUBLIC COMMENT, PLEASE HANG UP AND REJOIN IF YOU ARE HAVING SIDE CONVERSATIONS DURING THE MEETING

This meeting may be recorded to facilitate note-taking or other uses. By participating you consent to recording of your participation in this meeting.

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

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 (rxinfo@dhcfp.nv.gov). There may be opportunity to take public comment via telephone or the meeting's virtual platform as well as in person opportunities, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comment may be limited to three minutes per person. ***Note: this guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations****.*

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 April 22, 2021.
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 Antimigraine Medications - 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 Duchenne Muscular Dystrophy 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 Q4 2020 and Q1 2021 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q1 2021.
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 Division of Health Care Financing and Policy. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701).

If you require a physical copy of supporting material for the public meeting, please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701). Limited copies of materials will also be available on site at the meeting's physical location. Supporting material will also be posted online ~~as referenced above~~at http://dhcfp.nv.gov/ and https://www.medicaid.nv.gov/providers/rx/dur/DURBoard.aspx/.

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

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at rxinfo@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701.

Summary of the DUR Board

Drug Use Review Board

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

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

The DUR Board meets quarterly to monitor drugs for:

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

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

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

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

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair

Netochi Adeolokun, Pharm.D., Vice Chair

Mark Canty, MD

Crystal Castaneda, MD

Jessica Cate, Pharm.D.

Dave England, Pharm.D.

Brian Le, DO

Michael Owens, MD

Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2021

Date	Time	Location
July 22, 2021	1:00 PM	Surestay Plus Hotel – Reno, NV
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, April 22, 2021

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 1:13 p.m. on April 22, 2021. The roll was taken by Chairwoman Wheeler. Jennifer Wheeler, Pharm.D., Chair: Present ☒ Absent ☐ Netochi Adeolokun, Pharm.D., Vice Chair: Present ☒ Absent ☐ Mark Canty, MD: Present ☒ Absent ☐ Crystal Castaneda, MD: Present ☐ Absent ☒ Jessica Cate, Pharm.D.: Present ☒ Absent ☐ Dave England, Pharm.D.: Present ☒ Absent ☐ Mohammad Khan, MD: Present ☐ Absent ☒ Brian Le, DO: Present ☐ Absent ☒	**The DHCFP Staff Present were as follows:** Gudino, Antonio, Social Services Program Specialist III Lither, Gabriel, Senior Deputy Attorney General Flowers, Ellen, Program Officer I Olsen, David, Chief, Pharmacy Services Slamowitz, Beth, Pharm.D., Senior Policy Advisor on Pharmacy

Agenda Item	Record			Notes
	Michael Owens, MD	☒	☐	**Managed Care Organization representatives present were as follows:** Bitton, Ryan, Pharm.D., Health Plan of Nevada Lim, Luke, Pharm.D., Anthem Blue Cross Beranek, Tom, RPh, SilverSummit Health Plan **Gainwell Technology Staff Present were as follows:** Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Jeffery, Carl, Pharm.D. Piccirilli, Annette Hansen, Sean Medina, Daniel Kiriakopoulos, Amanda, Pharm.D. Whittington, Kevin, RPh **The public attendee list is 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.
	Jim Tran, Pharm.D.	☐	☒	
	A quorum was present.			

Agenda Item	Record	Notes
2. General Public Comment	Dr. Jeffery announced the meeting is being recorded. Telephonic and web comments were called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
3. Administrative		
a. **For Possible Action**: Review and Approve Meeting Minutes from January 28, 2021	No corrections were offered. Board Member Canty moved to approve the minutes as presented, and Board Member Adeolokun seconded the motion. A vote was taken, and the results were as follows from members in attendance (in favor, against, and abstentions where applicable): Jennifer Wheeler, Pharm.D., Chair: Yes ☒ No ☐ Abst. ☐ Netochi Adeolokun, Pharm.D., Vice Chair: Yes ☒ No ☐ Abst. ☐ Mark Canty, MD: Yes ☒ No ☐ Abst. ☐ Jessica Cate, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Dave England, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Michael Owens, MD: Yes ☒ No ☐ Abst. ☐	
b. Status Update by DHCFP	Mr. Antonio Gudino updated the Board on the updated prior authorization process for Zolgensma, explaining all requests for members enrolled in a managed care plan will be reviewed by the State. Mr. Gudino announced the implementation of the electronic prior authorization system available through the web portal or the provider's medical records software. Mr. Gudino	

Agenda Item	Record	Notes
	offered well wishes and appreciation to Dr. Khan, who is leaving the Board.	
4. Clinical Presentations		
a. **For Possible Action**: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Multiple Sclerosis (MS) Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery presented information regarding Kesimpta, including the indication, administration, and clinical trials demonstrating efficacy. Dr. Jeffery indicated no claims have been received for Kesimpta. Dr. Jeffery reviewed the proposed criteria presented in the binder. Dr. Lim agreed with the proposed criteria and reviewed the utilization. Dr. Bitton agreed with the proposed criteria and reviewed the utilization. Mr. Beranek agreed with the proposed criteria and reviewed the utilization.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	

Agenda Item	Record	Notes
iv. Proposed adoption of updated prior authorization criteria	Board Member England moved to approve the proposed criteria as presented, and Board Member Canty seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Jessica Cate, Pharm.D. ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐	
b. **For Possible Action**: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Hereditary Angioedema Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery summarized hereditary angioedema signs and symptoms. Dr. Jeffery presented the different products within the class, indications, and the proposed criteria. Dr. Jeffery outlined the utilization. Dr. Lim approved the criteria as presented and identified low utilization of the class.	

Agenda Item	Record	Notes
	Dr. Bitton approved the criteria as presented, and identified low utilization of the class. Mr. Beranek proposed a policy update to limit a member to one agent within the class at a time. Mr. Beranek identified the low utilization of the class.	
iii. Discussion by Board and review of utilization data.	Dr. Jeffery outlined the proposed changes to the Chapter 1200 criteria. Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria	Board Member Owens moved to accept the criteria as presented and Board Member Adeolokun seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ Yes ☐ No ☐ Abst. Mark Canty, MD ☒ Yes ☐ No ☐ Abst. Jessica Cate, Pharm.D. ☒ Yes ☐ No ☐ Abst. Dave England, Pharm.D. ☒ Yes ☐ No ☐ Abst. Michael Owens, MD ☒ Yes ☐ No ☐ Abst.	
c. **For Possible Action**: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Platelet Inhibitors.		

Agenda Item	Record	Notes
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery discussed utilization in the class and presented the criteria without changes for the Board to reaffirm the criteria. Dr. Lim proposed no changes and discussed the utilization of the class. Dr. Bitton proposed no changes and discussed the utilization of the class. Mr. Beranek proposed no changes and discussed the utilization of the class.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member Adeolokun moved to accept the criteria without changes, and Board Member Owens seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair — Yes ☒ No ☐ Abst. ☐ Netochi Adeolokun, Pharm.D., Vice Chair — Yes ☒ No ☐ Abst. ☐ Mark Canty, MD — Yes ☒ No ☐ Abst. ☐ Jessica Cate, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Dave England, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Michael Owens, MD — Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
d. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Narcolepsy Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. Comment was offered by Deb Profant with Jazz Pharmaceuticals on behalf of Xywav. Ms. Profant highlighted the indication, dosage, benefits of reduced sodium intake with Xywav and requested the prior authorization criteria be consistent with Xyrem. The following written public comment is attached hereto: 1. Written testimony for Xywav as read by Deb Profant with additional references. The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery. No further public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery highlighted Xywav's indications, dosage, similarities with Xyrem, and clinical trials demonstrating efficacy. Dr. Jeffery described the utilization of the class. Dr. Lim agreed with the proposed criteria and highlighted the utilization of the class. Dr. Bitton agreed with the proposed criteria and highlighted the utilization of the class.	

Agenda Item	Record	Notes
	Mr. Beranek agreed with the proposed criteria and highlighted the utilization of the class. Dr. Jeffery outlined the proposed changes to the prior authorization criteria as presented in the binder.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member Adeolokun moved to accept the criteria as presented and Board Member Owens seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ Yes ☐ No ☐ Abst. Mark Canty, MD ☒ Yes ☐ No ☐ Abst. Jessica Cate, Pharm.D. ☒ Yes ☐ No ☐ Abst. Dave England, Pharm.D. ☒ Yes ☐ No ☐ Abst. Michael Owens, MD ☒ Yes ☐ No ☐ Abst.	
e. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Anti-Hepatitis Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. Comment was offered by Laura Hill with AbbVie asked to clarify Appendix A for the Mavyret criteria for genotypes 1, 2, 3, 4, 5, or 6 for treatment-naive patients with compensated cirrhosis, the	

Agenda Item	Record	Notes
	current duration of treatment is 12 weeks but the labeled duration for that population is eight weeks. No further public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery summarized the proposed changes to remove the products that are no longer available and the references in the criteria. Dr. Jeffery highlighted the limited utilization. Dr. Lim agreed with the proposed criteria and summarized the declining utilization of products in the class. Dr. Bitton agreed with the proposed criteria and highlighted the utilization. Mr. Beranek agreed with the proposed criteria and highlighted the utilization. Dr. Jeffery highlighted the proposed changes to remove Daklinza, Olysio, Technivie, and Viekira XR and change the Mavyret treatment duration to eight weeks for genotypes 1, 2, 3, 4, 5, or 6 for treatment naïve patients with compensated cirrhosis.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria	Board Member England moved to accept the proposed criteria with the addition of changing the treatment duration to eight weeks as indicated. Board Member Adeolokun seconded the motion. A vote was held: Yes No Abst. Jennifer Wheeler, Pharm.D., Chair ☒ ☐ ☐	

Agenda Item	Record	Notes
	Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Jessica Cate, Pharm.D. ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐	
f. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. Comment was offered by Laura Hill with AbbVie on behalf of Ubrelvy, advocating for the removal of the triptan trial requirement due to not being effective and frequently pushing members to opioids. Comment was offered by Dr. Morton advocating for Ubrelvy. Dr. Morton highlighted the decreased butalbital, barbiturates, and opioids in migraine patients when treated with Ubrelvy, and efficacy and compliance are improved over the alternatives. Comment was offered by Maria Agapova with Teva Pharmaceuticals advocating for Ajovy. Ms. Agapova referenced submitted written documentation advocating for first-line treatment with CGRP agents and asked the Board to allow access to Ajovy as first-line treatment for migraine.	

Agenda Item	Record	Notes
	Comment was offered by Ben Droese with Amgen Medical Affairs advocating for Aimovig. Mr. Droese highlighted the indication, mechanism of action, administration, adverse reactions, clinical trials demonstrating efficacy and asked for Aimovig to be added to the preferred drug list. Comment was offered by [indiscernible name], a neurologist in Las Vegas advocating for Ubrelvy, stating it is effective and asked for open access. The following written public comment is attached hereto: 1. An information sheet for Aimovig was provided by Amgen. The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery. No further public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery highlighted the addition of Nurtec ODT to the existing criteria and outlined the utilization of the class. Dr. Lim agreed with the proposed criteria and highlighted the increasing utilization, especially with oral products. Dr. Bitton recommended adding criteria to fail two triptans and requiring additional options for chronic migraine treatment. Dr. Bitton highlighted the increase in utilization. Mr. Beranek recommended adding criteria to limit combinations of CGRP medications. Mr. Beranek highlighted the increasing trend of the medications in the class.	

Agenda Item	Record	Notes
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria	Board Member Adeolokun moved to accept the criteria as presented and Board Member Canty seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ Yes ☐ No ☐ Abst. Mark Canty, MD ☒ Yes ☐ No ☐ Abst. Jessica Cate, Pharm.D. ☒ Yes ☐ No ☐ Abst. Dave England, Pharm.D. ☒ Yes ☐ No ☐ Abst. Michael Owens, MD ☒ Yes ☐ No ☐ Abst.	
g. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Anticonvulsants.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comments were called for, and the phone lines were opened. Comment was offered by Raj Sandhar with UCB speaking on behalf of Briviact. Mr. Sandhar highlighted the costs of epilepsy, dosing of Briviact, indication, mechanism of action, clinical trials demonstrating efficacy, and asked for open access for Briviact. Comment was offered by Debbie Sheppe with Neurelis speaking on behalf of Valtoco. Ms. Sheppe asked for the removal of the requirement of rectal diazepam trial before approval of Valtoco.	

Agenda Item	Record	Notes
	Ms. Sheppe highlighted the indication, administration, safety information, and superior aspects compared to rectal diazepam gel. Comment was offered by Stephanie Kennedy with Greenwich Biosciences speaking on behalf of Epidiolex. Ms. Kennedy highlighted the indication, clinical trials demonstrating efficacy, and adverse reactions. Ms. Kennedy asked for the criteria to include the TSC indications and removal of the four seizure per month requirement. Comment was offered by Saveen Bangalore, a neurologist in Las Vegas, asking for open access to all antiepileptic medications. Comment was offered by Rachael Gardner a nurse practitioner in Reno speaking on behalf of Briviact. Ms. Gardner advocated for coverage of branded medications and asked for open access to antiepileptic medications. The following written public comment is attached hereto: 1. A list of bullet points advocating for Valtoco supplied by Neurelis. 2. An undated letter from the Hundley Foundation advocating for open access to all antiepileptic medications. 3. Written testimony for Briviact as read by Raj Sandhar advocating for open access to Briviact. 4. Written testimony for Epidiolex as read by Stephanie Kennedy advocating for the additional diagnosis of TSC be added and removal of the four seizures per month requirement.	

Agenda Item	Record	Notes
	5. A letter dated April 4, 2021, from Dr. Gerardo Rodriguez-Gomez advocating for open access to all antiepileptic medications. The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery. No further comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery highlighted the purpose of the review is to remove the requirement for consideration of rectal diazepam before approval of Valtoco. Dr. Jeffery discussed the utilization of the medications in the class. Dr. Lim agreed with the proposed criteria and highlighted the utilization. Dr. Bitton agreed with the proposed criteria and highlighted the utilization. Mr. Beranek recommended adding criteria for members to be stabilized on antiepileptic medications prior to Valtoco use. Mr. Beranek highlighted the utilization. Dr. Jeffery discussed the TCS indication is already included in the updated Medicaid Services Manual, and there is no prior authorization requirement for Briviact. Dr. Jeffery highlighted the only change includes removing the requirement to consider rectal diazepam for Valtoco approval.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	

Agenda Item	Record	Notes
iv. Proposed adoption of updated prior authorization criteria	Board Member Adeolokun moved to accept the criteria as presented and Board Member Owens seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair — Yes ☒ No ☐ Abst. ☐ Netochi Adeolokun, Pharm.D., Vice Chair — Yes ☒ No ☐ Abst. ☐ Mark Canty, MD — Yes ☒ No ☐ Abst. ☐ Jessica Cate, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Dave England, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Michael Owens, MD — Yes ☒ No ☐ Abst. ☐	
5. DUR Board Requested Reports		
a. **For Possible Action**: Opioid utilization – top prescriber and members		
i. Discussion by the Board and review of utilization data.	Dr. Jeffery presented the opioid utilization identifying the consistent decline of total morphine equivalent dose (MED). Dr. Jeffery pointed out a few members with high MED due to fentanyl utilization. Dr. Jeffery highlighted the top prescribers sorted by total MED and MED per member per day supply. Dr. Jeffery described the student specialty on the last report as a residency program. Dr. Lim presented the opioid utilization identifying a steady MED over time with a small increase in December. Dr. Lim discussed the top providers and top utilizers and pointed out high utilization of oxycodone immediate release. Dr. Bitton presented the opioid utilization trends with an increase in claim count due to an increase in membership. Dr. Bitton discussed the top prescribers and top members and how the two lists correlate.	

Agenda Item	Record	Notes
	Mr. Beranek presented the opioid utilization with a slight increase in December, the top opioid prescribers by claim count, and top members who are consistent over the year.	
ii. Requests for further evaluation of proposed clinical criteria to be presented at a later date.	The Board made no requests.	
6. Standard DUR Reports		
a. Review of Prescribing/Program Trends.		
i. Top 10 Therapeutic Classes for Q3 2020 and Q4 2020 (by Payment and by Claims).	Dr. Jeffery presented the top classes with similar results over the quarter with hemostatics on the top by spend amount and anticonvulsants in the top by claim count. Dr. Lim presented the top classes and identified fourth quarter was higher due to the additional membership. Dr. Bitton presented the top classes and identified the consistent amounts in the two quarters. Mr. Beranek presented the top drug classes and identified the consistency over the two quarters.	
b. Concurrent Drug Utilization Review (ProDUR).		
i. Review of Q4 2020. ii. Review of Top Encounters by Problem Type.	Dr. Jeffery highlighted the prospective DUR reports and the interventions but nothing to report out of the ordinary. Dr. Lim discussed the prospective DUR edits. Dr. Bitton pointed out the prospective DUR report without anything out of the ordinary.	

Agenda Item	Record	Notes
	Mr. Beranek called out some differences in the prospective DUR compared to other programs but nothing unexpected.	
c. Retrospective Drug Utilization Review (RetroDUR).		
i. Status of previous quarter. ii. Status of current quarter. iii. Review and discussion of responses.	Dr. Jeffery discussed the retrospective DUR initiatives during the last quarter with continuous glucose monitors and albuterol use without a preventative inhaler. Dr. Lim highlighted the retrospective DUR programs, including asthma and behavioral health programs, and their respective outcomes. Dr. Bitton highlighted retrospective DUR initiatives and results, calling out cardiovascular and diabetes initiatives. Mr. Beranek discussed the retrospective DUR program highlighting the opioid program for high opioid prescribers.	
7. Closing Discussion		
a. Public Comment	Telephonic and web comments were 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 July 22, 2021, and the location is yet to be determined.	
c. Adjournment	The meeting adjourned at 3:03 p.m.	

Attachment A – Member of the Public in Attendance

Aholt, Kevin
Agapova, Maria, Teva
Bailey, Alan, UCB
Bala, Kaysen, Biogen
Bangalore, Saveen
Bannach, Stacey, Gilead
Behnken, Heather, UCB
Booth, Robert, AbbVie
Cardenas, Natalie, UCB

Cochrane, Tim M, Gilead
Colabianchi, Jeana, Sunovion
Cooper, Christa, Lilly
DeFelice, Elaine, UCB
Delgado, Jonathan, Novonordisk
Droese, Ben, Amgen
Duke, Michelle
Einbinder, Karen, Greenwich Pharmaceuticals
Gardner, Rachael
Gaynor, Jennifer
George, Laura
Germain, Joe, Jr., Biogen
Gorzynski, Andrew, Novartis
Gouchenour, Christie, Hometown Health
Grothe, Deron, TevaHertzberg, Susan
Hill, Laura L, AbbVie
Isaki, Steven, Lundbeck
Jackson, Karen, Trividia Health
Kennedy, Stephanie, Greenwich Pharmaceuticals
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Knisley, Evie, Novartis
Kopp, Adam
Large, David, Biohaven Pharmaceuticals
Leroue, Chelsea, Biohaven Pharmaceuticals
Oliver, Carmen, Biohaven Pharmaceuticals
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O'Neill, William, Sunovion
Pearce, Robert, Teva
Phillips, Katherine, Jazz Pharmaceuticals
Profant, Deb, Jazz Pharmaceuticals
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Robinson, Lovell R, Abbvie
Sandhar, Raj, UCB
Santarone, Christopher, BMS
Semenchuk, Marilyn
Sheppe, Debbie, Pharm.D., Neurelis
Smith, Nathan, UCB
Swett, Alice
Taylor, Trent, Johnson and Johnson
Tran, Jim
Wolin, Jonathan
Yamashita, Kelvin, Sanofi
Attendees with no last name available:
Chris
Joe

Clinical Presentations

Prior Authorization Guideline

Guideline Name Dihydroergotamine

1 . Indications

Drug Name: D.H.E. 45 (dihydroergotamine mesylate) injection
Migraine Indicated for the acute treatment of migraine headaches with or without aura. **Cluster Headache** Indicated for the acute treatment of cluster headache episodes.
Drug Name: Migranal (dihydroergotamine mesylate) nasal spray
Migraine Indicated for the acute treatment of migraine headaches with or without aura. Not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

2 . Criteria

Product Name: Brand D.H.E. 45 injection, Generic dihydroergotamine mesylate injection, Brand Migranal nasal spray, or Generic dihydroergotamine mesylate nasal spray	
Diagnosis	Migraines
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of migraine headaches with or without aura	

AND

2 - Will be used for the acute treatment of migraine

AND

3 - Patient is 18 years of age or older

AND

4 - One of the following:

- Trial and failure or intolerance to two triptans (e.g., eletriptan, rizatriptan, sumatriptan)
- Contraindication to all triptans

AND

5 - If patient has 4 or more headache days per month, patient must meet one of the following:

5.1 Currently being treated with Elavil (amitriptyline) or Effexor (venlafaxine) unless there is a contraindication or intolerance to these medications

OR

5.2 Currently being treated with Depakote/Depakote ER (divalproex sodium) or Topamax (topiramate) unless there is a contraindication or intolerance to these medications

OR

5.3 Currently being treated with a beta blocker (i.e., atenolol, propranolol, nadolol, timolol, or metoprolol) unless there is a contraindication or intolerance to these medications

AND

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

- Neurologist
- Pain specialist
- Headache specialist

Product Name: Brand D.H.E. 45 injection, Generic dihydroergotamine mesylate injection, Brand Migranal nasal spray, or Generic dihydroergotamine mesylate nasal spray	
Diagnosis	Migraines
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient has experienced a positive response to therapy (e.g., reduction in pain, photophobia, phonophobia, nausea)

AND

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

- Neurologist
- Pain specialist
- Headache specialist

Product Name: Brand D.H.E. 45 injection or Generic dihydroergotamine mesylate injection	
Diagnosis	Cluster Headaches
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of cluster headache

AND

2 - Patient is 18 years of age or older

AND

3 - Trial and failure, contraindication, or intolerance to sumatriptan injection

AND

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

- Neurologist
- Pain specialist
- Headache specialist

Product Name: Brand D.H.E. 45 injection or Generic dihydroergotamine mesylate injection	
Diagnosis	Cluster Headaches
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

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

AND

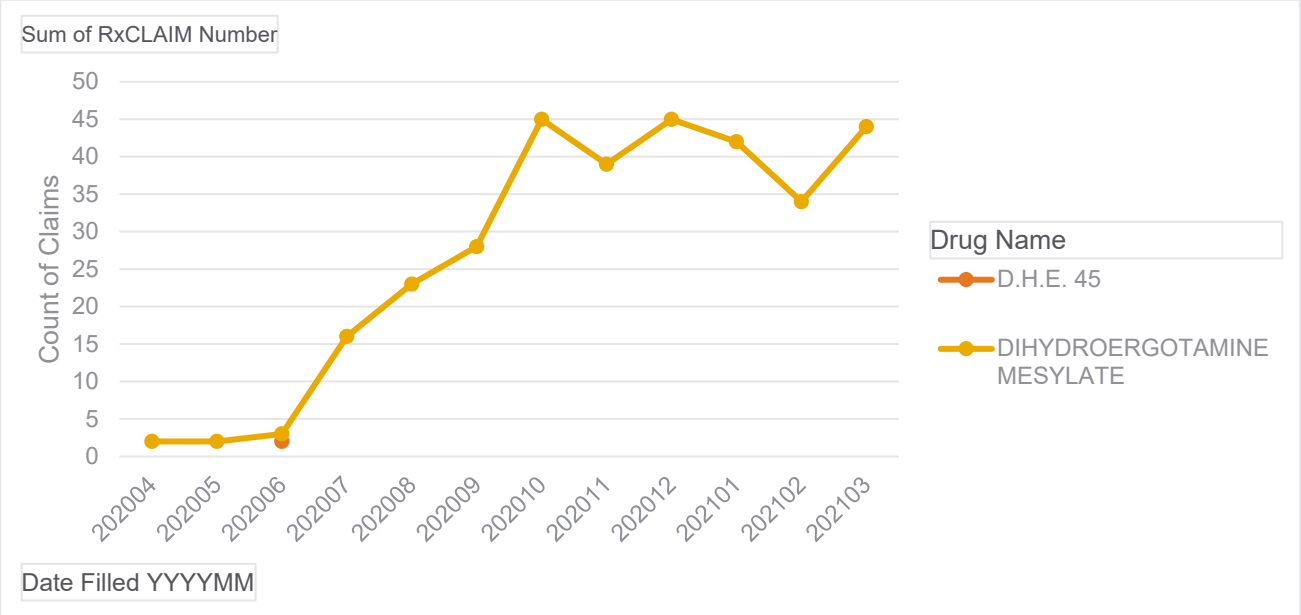
2 - Prescribed by or in consultation with one of the following specialists:

- Neurologist
- Pain specialist
- Headache specialist

Nevada Medicaid

Antimigraine Medications - Miscellaneous
Fee for Service
April 1, 2020 – March 31, 2021

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
D.H.E. 45	2	2	2	55
DIHYDROERGOTAMINE MESYLATE	78	323	9,481	2,576



Therapeutic Class Overview
Anti-Migraine agents, miscellaneous

INTRODUCTION

- Migraine is a disabling, episodic, primary headache disorder. Worldwide, it affects over 1 billon people and is considered the leading cause of disability in people younger than 50 years old. Individuals with a family history of migraine are more susceptible to developing them, and female sex is a risk factor of migraines that can persist into adulthood; in general migraine headaches are more common in adult women than men (17% vs 6%) *(Ashina et al 2021*, *Cutrer et al 2020, International Headache Society [IHS] 2018, Oskoui et al 2019).*
- Migraines are categorized into 2 types: with aura or without aura. Migraines without aura are more common and account for approximately 75% of cases (*Cutrer et al 2020, IHS 2018).*
  - Migraine attacks typically last between 4 and 72 hours in adults, and usually progress through 4 phases: the prodrome, the aura (occurring in approximately 25% of individuals), the headache, and the postdrome.
  - Factors that may trigger a migraine can include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame.
- Tension-type headaches (TTH) is the most prevalent type of headache, affecting 30 to 78% of the general population, and is one of the most common reasons why individuals purchase over the counter analgesics. TTH can be further categorized into episodic (frequent or infrequent) and chronic types; common features include mild to moderate intensity, bilateral pressing or tightening (non-pulsating), and usually does not cause nausea, vomiting, photophobia, phonophobia that is commonly seen with migraines (*IHS 2018, Taylor 2020[a], Taylor 2020[b]*).
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen [APAP]), and moderate to severe attacks are treated more migraine specific agents including triptans, calcitonin gene-related peptide (CGRP) antagonist or other agents. The use of ergot alkaloids has been largely displaced with the advent of triptans for acute treatment (*Smith 2021*, *Tfelt-Hansen 2013*).
- The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, aspirin [ASA]) followed by combination analgesics containing caffeine plus a simple analgesic. The efficacy of the simple analgesics tends to decrease with increasing frequency of the headaches (*Taylor 2020[b], Bentsen et al 2010*).
- Avoiding medication overuse headache (MOH) is an important goal of acute therapy and can occur when primary headache disorders (eg, migraine, tension-type) have been treated with excessive amounts of acute symptomatic medications. The risk of developing MOH appears to be highest with opioids, butalbital-containing combination analgesics, and analgesic-caffeine combinations; thus guidelines recommend against their use due to this (*Bendtsen et al 2010, Garza 2019, Silberstein and McCrory et al 2001, Smith 2021*).
  - In order to prevent the development of MOH, most acute medications should be limited to less than 10 days per month (or less than 15 days per month for ASA, APAP, and NSAIDs), and preventive therapies should be used as the mainstay in patients with frequent headaches.
- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies, which may be in part due to insufficient outcomes reporting in early trials and inconsistencies in demonstrating statistically significant differences in headache relief, and the lack of more recent clinical trials (*Tfelt-Hansen 2000, Silberstein and McCrory 2003)*. Additionally, ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism, and caffeine enhances its absorption; levels are slightly higher with rectal administration. Similarly, dihydroergotamine (DHE) also goes through extensive first pass metabolism, thus intranasal (IN) and intravenous (IV) administration bypass this and can deliver adequate plasma concentrations (*Silberstein and McCrory 2002*).
- Reyvow (lasmiditan) is a first in class 5-hydroxytryptamine (5-HT)1F receptor agonist for acute treatment of migraine attacks (triptans are 5-HT 1b/1d agonists) approved in 2019 by the Food and Drug Administration (FDA). This newer agent may play a role in patients with cardiovascular (CV) contraindications to triptans due to lack of vasoconstrictor activity (*AHS 2019*). In January 2021, the Drug Enforcement Agency (DEA) published a final rule placing lasmitidan as a Schedule V drug based on human abuse potential studies demonstrating significantly higher scores for drug liking, euphoric mood and feelings of relaxation (*Reyvow prescribing information 2021*).

- The focus of this overview will be migraine treatments including ergot alkaloids, butalbital combination products and Reyvow (lasmiditan). Injectable formulations have been excluded from this review. Codeine containing combination products are reviewed in the short acting opioids TCO.
- Medispan classes: Ergot combinations; Migraine products – ergotamine, dihydroergotamine; Analgesic combinations; Selective serotonin agonists 5-HT(1F)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cafergot (ergotamine/caffeine) tablets	✔
Migergot (ergotamine/caffeine) rectal suppository	-
Ergomar (ergotamine tartrate) sublingual tablets	-
Migranal (dihydroergotamine mesylate) nasal solution	✔
Allzital, Bupap, Tencon (butalbital/APAP) tablets or capsules	✔
Fioricet, Vtol LQ (butalbital/caffeine/APAP) capsules or oral solution	✔
Fiorinal (butalbital/caffeine/ASA) tablets	✔
Reyvow (lasmiditan) tablets	-

Abbreviations: APAP = acetaminophen, ASA = aspirin

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cafergot (ergotamine/ caffeine)	Migergot (ergotamine/ caffeine)	Ergomar (ergotamine tartrate)	Migranal (dihydroergotamine mesylate)	Allzital, Bupap, Tencon (butalbital/APAP) *	Fioricet, Vtol LQ (butalbital/caffeine/ APAP) *	Fiorinal (butalbital/ caffeine/ASA)	Reyvow (lasmiditan)
Therapy to abort or prevent vascular headache (eg, migraine, migraine variants, or so-called "histaminic cephalalgia").	✔	✔	✔					
Acute treatment of migraine headaches with or without aura.				✔				✔ †
For the relief of the symptom complex of tension (or muscle contraction) headache					✔	✔	✔	

Abbreviations: APAP = acetaminophen, ASA = aspirin

Note: Safety and effectiveness of butalbital-containing products have been established in children aged 12 years and older.

* Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

† Limitation of use: not indicated for the preventative treatment of migraine.

(*Prescribing information: Allzital 2020, Bupap 2020, Cafergot 2019, Migergot 2019, Ergomar 2020, Fioricet 2021, Fiorinal 2018, Vtol LQ 2019, Migranal 2019, Tencon 2017, Reyvow 2021*)

- 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

Ergot alkaloids

- Currently, ergotamine can be used in patients with frequent, moderate migraine but have been found to be less effective than triptans; in 3 head-to-head randomized controlled trials (RCTs), oral triptans (sumatriptan, eletriptan, and rizatriptan) were superior to oral ergotamine 2 mg plus caffeine 200 mg for quicker onset of headache relief and pain freedom at 2 hours . Sumatriptan, however was associated with higher incidence of headache recurrence at 48 hours (*Christie et al 2003, Diener et al 2002, The Multinational Oral Sumatriptan and Caferget Comparative Study Group 1999, Worthington et al 2013).* An early comparator trial demonstrated non-inferiority of ergotamine vs other migraine treatments such as naproxen, but with more adverse effects (AEs) such as nausea (*Sargent et al 1988*).
- A crossover (XO), double-blind trial (DB; N = 272) compared almotriptan vs ergotamine plus caffeine for acute migraine therapy; The primary endpoint was the proportion of patients achieving pain freedom at 2 hours. Patients were instructed to treat 2 migraine attacks, 1 with almotriptan 12.5 mg and the other with ergotamine 2 mg plus caffeine 200 mg. Rescue medication could be used 2 or more hours after treatment with the study drug for persistent moderate to severe pain and recurrence medication (the study medication for that attack) was allowed for patients who initially responded to the study medication but experienced a recurrence or worsening of their migraine during the first 48 hours after taking the study medication (*Láinez et al 2007*).
  - Treatment with almotriptan was associated with a significantly greater proportion of patients achieving pain freedom at 2 hours vs ergotamine plus caffeine (20.9% vs 13.7%; $p < 0.05$).
  - The XO design also assessed the benefit of one treatment over the other demonstrating that of the 20.9% who achieved pain freedom at 2 hours with almotriptan, 29% also responded to ergotamine plus caffeine; of the 13.7% who achieved pain freedom at 2 hours with ergotamine plus caffeine, 44% responded to almotriptan.
  - The study was not powered to detect the differences in safety between almotriptan vs ergotamine plus caffeine.
- A network meta-analysis (NMA) of 141 RCTs (7 studies including ergotamines) evaluated the comparative tolerability of various treatments including triptans, NSAIDs, and ergotamines, in any combination with or without caffeine or barbiturates for acute migraine. The primary outcomes were any AE, treatment-related AEs, and serious AEs. Overall, triptans and ergotamine were both associated with higher odds of any AE compared with NSAIDs, while tolerability profiles were mixed and comparable across various treatments (*Thorlund et al 2017*).
- DHE (Migranal) IN was shown to be effective in 4 RCTs. Patients treated a single moderate to severe migraine headache with a single dose of DHE IN (or placebo) and assessed pain severity over the 24 hours. Following treatment, the percentage of patients achieving headache response (rather than pain freedom) was reported at 2 hours as significant in Study 1 ($p < 0.001$) and at 4 hours in Studies 2 ($p < 0.01$), 3 ($p < 0.001$) and 4 ($p < 0.001$) (*Migranal prescribing information 2019*).
  - An analysis of 4 RCTs comparing DHE IN to placebo found a statistically significant effect size in favor of DHE (0.34; 95% confidence interval [CI], 0.10 to 0.57). This is particularly important for patients with moderate to severe attacks who are unable to tolerate oral medications due to nausea and vomiting (*Silberstein and McCrory 2003).*
  - A systematic review (SR) and meta-analysis (MA) evaluated the use of sumatriptan IN for acute migraine attacks. One study was compared to DHE IN in terms of safety and found no significant difference between both groups in terms of the incidence of all AEs within 24 hours ($p = 0.97$) or withdrawal due to AEs ($p = 0.30$) (*Menshawy 2018*).
- Several comparative effectiveness studies have evaluated the efficacy of triptans vs ergot derivatives for the acute treatment of migraines.
  - In a multicenter, DB, double placebo, XO study compared sumatriptan subcutaneous (SC) to DHE IN and found that sumatriptan was significantly better at providing both headache relief at 2 hours and resolution ($p < 0.001$ for both endpoints). However, more AEs were reported with sumatriptan SC (43%) vs DHE IN (22%) and fewer patients experienced headache recurrence with DHE IN (31% vs 17% with sumatriptan) (*Touchon et al 1996, Worthington et al 2013*).
  - Two Cochrane reviews evaluated sumatriptan (SC and IN) to DHE nasal spray. Results of the included studies demonstrated a higher proportion of patients being pain free at 2 hours with sumatriptan SC vs DHE nasal spray, while the efficacy data comparing sumatriptan IN to DHE nasal spray was deemed unusable. Overall, there was insufficient data available to carry out pooled analyses for any outcomes of interest to draw firm conclusions regarding efficacy between treatments (*Derry et al 2012[a], Derry et al 2012[b]).* One SR considered the 2 Cochrane reviews,

among other individual studies and found DHE IN has variable to superior efficacy vs placebo in acute migraine; however, it was less effective then IN or SC sumatriptan (*Worthington et al 2013*).

Butalbital combinations – Fioricet (butalbital/caffeine/APAP) and Fiorinal (butalbital/caffeine/ASA)

- Recent clinical trials evaluating butalbital combination products (eg, butalbital/caffeine/APAP and butalbital/caffeine/ASA) for TTH are not available.
- One study has evaluated the efficacy of butalbital-containing agent for migraine headaches vs placebo and FDA-approved anti-migraine triptan medication. A Phase 3 RCT in 503 patients (88% were currently using a butalbital-containing drug) with migraine headache that severely impacted their life, directly compared Fioricet vs sumatriptan-naproxen vs placebo. The primary endpoint was the percentage of treated attacks with sustained pain free (SPF) response 2 to 24 hours after treatment with sumatriptan-naproxen vs Fioricet. SPF was defined as being pain-free from 2 through 24 hours after initial dosing without return of migraine pain or use of any rescue medication. Results demonstrated no difference in the primary endpoint between Fioricet vs sumatriptan-naproxen (6% vs 8%; OR, 1.3; p = 0.378). However, when each drug was compared to placebo, sumatriptan-naproxen was shown to have better pain relief compared to Fioricet for the secondary endpoints of pain-free, pain relief, migraine-free, complete symptom-free, and pain-free with relief of nausea, photophobia, phonophobia, and sinus/facial pain at most time points (*Derosier et al 2011, Worthington et al 2013*).

Reyvow (lasmiditan)

- The efficacy of lasmiditan in the acute treatment of migraine with or without aura was demonstrated in 2 Phase 3, DB, placebo controlled (PC) RCT trials, SAMURAI and SPARTAN (*Kuca et al 2018*, *Goadsby et al 2019*). Both studies included patients with CV risk factors, but SPARTAN included patients with known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. The efficacy of lasmiditan was evaluated in terms of pain freedom (defined as a reduction of moderate or severe headache pain to no pain) and Most Bothersome Symptom (MBS) freedom (defined as the absence of the self-identified MBS [photophobia, phonophobia, or nausea]) at 2 hours compared to placebo (*Reyvow Prescribing Information 2020*). In both studies, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo.
  - In SAMURAI (N = 1856), lasmiditan pain freedom at 2 hours dosing (200 mg: 32.2%; OR, 2.6, 95% CI, 2.0 to 3.6; p < 0.001; lasmiditan 100 mg: 28.2%; OR 2.2, 95% CI, 1.6 to 3.0; p < 0.001) vs placebo (15.5%).
    - Freedom from MBS (lasmiditan 200 mg: 40.7%; OR, 1.6; 95% CI, 1.3 to 2.1; p < 0.001; lasmiditan 100 mg: 40.9%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001) vs placebo (29.5%).
  - In SPARTAN (N = 3005), lasmiditan pain freedom at 2 hours (lasmiditan 200 mg: 38.8%; OR, 2.3; 95% CI, 1.8 to 3.1; p < 0.001; lasmiditan 100 mg: 31.4%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001; lasmiditan 50 mg: 28.6%, OR, 1.5; 95% CI, 1.1 to 1.9; p = 0.003) vs placebo (21.3%),
    - Freedom from MBS (lasmiditan 200 mg: 48.7%, OR, 1.9; 95% CI, 1.4 to 2.4; p < 0.001; lasmiditan 100 mg: 44.2%; OR, 1.6; 95% CI, 1.2 to 2.0; p < 0.001; 50 mg: 40.8%; OR, 1.4; 95% CI, 1.1 to 1.8; p = 0.009) vs placebo (33.5%).
- GLADIATOR was an open label extension trial that randomized 2116 patients from SAMURAI and SPARTAN to receive lasmiditan 100 mg or 200 mg with the goal of evaluating long-term safety and efficacy (up to 1 year of intermittent use). A total of 962 patients (48.6%) reported ≥ 1 treatment emergent AE including dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%), similar to those in the pivotal trials. Dizziness was the most common AE leading to discontinuation (*Brandes et al 2019*).
- An analysis evaluated the safety and efficacy of a second dose of lasmiditan for rescue or headache recurrence found some evidence of efficacy when taken for headache recurrence, but there was no clear benefit of a second dose for rescue treatment (*Loo et al 2019*).
- A SR and MA of 3 RCTs (N=4,506) evaluated the safety and efficacy of lasmiditan for acute treatment of migraine. Overall, lasmiditan was associated with a significantly increased rate of patients experiencing pain freedom at 2 hours post-dose vs placebo (31.6% vs 17.55%), and freedom from MBS at 2 hours (42.82% vs 30.38%). However, lasmiditan was associated with higher rates of fatigue, paresthesia, and somnolence (*Yang et al 2020*). Another SR and MA of 4 RCTs (N = 4,960) concluded that while lasmiditan is effective for acute treatment of migraine, it is associated with a higher incidence of central nervous system (CNS) related side effects including dizziness, nausea, fatigue, paresthesia and somnolence (p < 0.00001 for all AEs) (*Hou et al 2020*).

- An Institute for Clinical and Economic Review (ICER) NMA of 33 RCTs evaluated the safety and efficacy of lasmiditan and oral CGRP antagonists (rimegepant and ubrogepant) for acute treatment of migraine to each other, placebo, and triptans. Results from PC clinical trials indicate that lasmiditan, rimegepant and ubrogepant decrease symptoms of migraine attacks (pain, phonophobia, photophobia, or nausea) and improve function compared to placebo at 2 hours, but all interventions showed lower odds of achieving pain freedom compared to triptans. Additionally, while similar rates of efficacy were demonstrated between the newer agents, lasmiditan had significantly higher rates of dizziness and discontinuation (*Atlas et al 2020*).

- The Agency for Healthcare Research and Quality (AHRQ) evaluated the comparative effectiveness of various pharmacotherapies used for the treatment of migraine headaches (*Halker Singh et al 2020*). Sixteen RCTs with 2,615 patients specifically studied the efficacy of ergotamine, with or without caffeine, as well as ergotamine vs placebo or lidocaine. Endpoints included pain free or pain relief at 2 hours, pain scale at 2 hours, restored function at 1 day, pain free at 1 day, pain relief at 1-day, sustained pain free at 1 week, and sustained pain relief at 1 week. Compared to placebo, DHE IN (2 mg and 3 mg) was more likely to lead to pain free and restore function at 2 hours and 1 day. Additionally, while compared to placebo, ergotamine plus caffeine probably improves pain relief at 2 hours, but a number of RCTs failed to demonstrate significant difference in headache relief compared to placebo and was associated with more AEs, mirroring early trials.
  - Five RCTs evaluated the efficacy of lasmiditan and demonstrated probable improvement in pain relief at 2 hours and increased likelihood of being pain free at 2 hours, 1 day, 1 week, and restored function vs placebo. However, serious gastrointestinal and neurological AEs were more common with lasmiditan vs placebo.

CLINICAL GUIDELINES

- The 2019 American Headache Society (AHS) position statement on integrating new migraine treatments (*AHS 2019*) recommends the use of NSAIDs, non-opioid analgesics, APAP, or caffeinated analgesic combinations for acute treatment of mild to moderate migraine attacks. For moderate to severe attacks, the guidelines suggests DHE or triptans that respond poorly to NSAIDs or caffeinated combination products.
  - Non-oral formulations are recommended if severe nausea or vomiting are associated with a migraine attack. This can include sumatriptan (IN or inhaled), ketorolac (IN or intramuscular), or DHE (IN or SC).
  - The guidelines indicate that emerging acute treatments for migraine headache such as the CGRP antagonists indicated for acute use, and the selective 5-HT_{1F} receptor agonist (lasmiditan) do not have vasoconstrictive effects; therefore, they may play a role in patients with CV contraindications to triptans. It is recommended that patients be eligible for these newer agents if they have contraindications to the use of triptans or have failed to respond to or tolerate ≥ 2 oral triptans.
  - To avoid medication overuse, patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 to 3 headache days per week, and if exceeding this limit, should be offered preventative treatment.
- The 2019 American Academy of Neurology and AHS guideline for the acute symptomatic treatment of migraine in children and adolescents (*Oskoui et al 2019*) recommends the use of ibuprofen, APAP (in children and adolescents) and triptans (mainly in adolescents) for the relief of migraine pain. Ergots alone have not been studied in children.
- The 2019 European Headache Federation aids to management of headache disorders in primary care (2nd edition) recommends a stepwise approach to treatment. This includes treating 3 attacks at each step before proceeding to the next (*Steiner et al 2019*).
  - Step 1: non-opioid analgesic plus an antiemetic (when needed).
    - Opioids are considered ineffective for migraine, and barbiturates (eg, butalbital) have no place in migraine treatment.
  - Step 2: Triptans; limited to ≤ 10 days per month.
    - Domperidone 10 mg can be added for nausea, and nasal spray or SC formulations can be used when vomiting is present.
    - ergotamine is considered a poor substitute for triptans due to low and unpredictable bioavailability, which impairs efficacy, and poor tolerability. It is no longer recommended for routine use.
  - Treatment of relapse: a repeat dose of triptan may be used, and any patient with migraine who is not well controlled on acute therapy should be offer prophylaxis in addition to acute medication.

- The 2013 Canadian Headache Society (CHS) guideline for acute drug therapy for migraine indicates that ergotamine use is problematic in migraine because of poor oral absorption, vasoconstrictive side effects, and the frequent occurrence of dose limiting side effects such as nausea, which make it difficult to achieve a therapeutic dose in patients. Thus, ergotamine is not recommended routinely for acute migraine pain. Additionally, the guideline strongly recommends avoiding the use of butorphanol and butalbital containing medications. Intranasal or SC DHE can be considered for acute treatment of moderate to severe attacks (*Worthington et al 2013*).
- The 2010 EFNS guideline for the treatment of tension headache (*Bendtsen et al 2010*) recommends the use of simple analgesics (eg, APAP, ASA, ibuprofen, naproxen, ketoprofen, diclofenac) for mild to moderate TTH. Second-line treatment includes a simple analgesic plus caffeine. The guideline recommends against the use of combination products with codeine or barbiturates due to the increased risk of developing MOH. Additionally, triptans most likely do not have a clinically relevant effect in patients with TTH and cannot be recommended.
- The 2009 European Federation of Neurological Societies (EFNS) guideline for the treatment of migraine (*Evers et al 2009)* recommends the use of NSAIDs and triptans for acute treatment of migraine attacks. In very severe attacks, IV ASA or SC sumatriptan are drugs of first choice.

SAFETY SUMMARY

- Cafergot, Migergot, Ergomar (ergotamine/caffeine)
  - **Boxed warning**: Co-administration with potent cytochrome P450 (CYP) 3A4 inhibitors can lead to elevated serum levels of ergotamine tartrate increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications:
    - Pregnancy and nursing: Category X, potential to cause fetal harm, oxytocic effects
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
  - Warnings and precautions
    - Co-administration with potent CYP3A4 inhibitors can lead to serious AEs.
    - Ergotism (intense arterial vasoconstriction), fibrotic complications with long term, continuous use.
    - Drug abuse and dependence with long term use.
  - AEs
    - Vasoconstrictive complications, nausea, vomiting, rectal or anal ulcers (from suppository overuse), local edema or itching (suppository use).
  - Key drug interactions: Potent CYP3A4 inhibitors (ie, macrolide antibiotics, protease inhibitors, fluconazole, grapefruit juice, fluoxetine)

- Migranal (dihydroergotamine mesylate)
  - **Boxed warning**: Co-administration with potent CYP3A4 inhibitors (ie, protease inhibitors, macrolide antibiotics) can lead to elevated serum DHE levels increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications
    - Co-administration with potent CYP3A4 inhibitors
    - Ischemic heart disease, coronary artery vasospasm (including Prinzmetal's variant angina),
    - Do not use within 24 hours of taking sumatriptan, ergotamine-containing or ergot-type medications, or methysergide.
    - Should not be used in patients with hemiplegic or basilar type migraines.
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
    - Pregnancy and nursing: Potential to cause fetal harm, oxytocic effects
    - Should not be used with peripheral or central vasoconstrictors due to synergistic elevation in blood pressure.
  - Warnings and precautions
    - Only use where a clear diagnosis of migraine has been established.
    - Co-administration with potent CYP3A4 inhibitors
    - Fibrotic complications
    - Risk of myocardial ischemia or infarction and other cardiac AEs and death have occurred. Patients with risk factors predictive of coronary artery disease (CAD) who have had a sufficient CV evaluation, should have the first dose of

DHE administered in a physician's office unless they have previously received it. Long term users of DHE should have regular CV evaluations.
    - Drug associated cerebrovascular events and fatalities
    - Increases in blood pressure
    - Local irritation
  - AEs: Rhinitis, pharyngitis, nausea, vomiting, altered sense of taste, application site reaction, dizziness.
  - Key drug interactions: Vasoconstrictors, sumatriptan, beta-blockers, nicotine.

- Bupap, Tencon, Allzital (butalbital/APAP) and Fioricet, Vtol LQ (butalbital/caffeine/APAP)
  - **Boxed warning**: Hepatotoxicity with the use of APAP > 4000 mg per day, and often occurs due to more than one APAP containing product taken at a time.
  - Contraindications: Hypersensitivity to any component, patients with porphyria.
  - Warnings and precautions
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended.
    - APAP: Hypersensitivity, anaphylaxis, serious skin reactions
  - AEs (most common): Drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.
  - Drug interactions: Alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.

- Fiorinal (butalbital/caffeine/ASA)
  - Contraindications
    - Hypersensitivity or intolerance to ASA, caffeine, or butalbital.
    - Patients with a hemorrhagic diathesis (eg, hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).
    - Patients with nasal polyps, angioedema and bronchospastic reactivity to ASA or other NSAID.
    - Peptic ulcer or other serious gastrointestinal lesions.
    - Patients with porphyria.
  - Warnings and precautions
    - ASA component: Anaphylaxis, bleeding risk
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended
  - AEs (most common): Drowsiness, dizziness

- Reyvow (lasmiditan)
  - Contraindications: None
  - Warnings and precautions: Driving impairment, CNS depression particularly in combination with alcohol or other CNS depressants, serotonin syndrome, medication overuse headache that may require detoxification.
  - AE (most common): Dizziness, fatigue, paresthesia, and sedation.
  - Key drug interactions
    - Heart lowering drugs: Reyvow may further lower heart rate when used concomitantly
    - Avoid concomitant use with P-glycoprotein and breast cancer resistant protein substrates.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cafergot (ergotamine/ caffeine)	Tablets	Oral	Two tablets at start of attack; 1 additional tablet	Maximum 6 tablets per attack or 10 tablets per week.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			every 30 minutes if needed.	Dose should start at the first sign of an attack.
Migergot (ergotamine/ caffeine) rectal suppository	Suppository	Rectal	One suppository at the start of attack; second suppository after 1 hour if needed for full relief.	Maximum 2 suppositories per attack, 5 suppositories per week. Should not be used for chronic daily administration.
Ergomar (ergotamine tartrate)	Sublingual tablets	Oral	One tablet at the start of an attack; 1 additional tablet every 30 minutes.	Maximum 5 tablets per attack or 10 tablets per week.
Migranal (dihydroergotamine mesylate)	Nasal solution	Nasal	Four sprays; 1 spray in each nostril; 1 additional spray in each nostril after 15 minutes	Maximum 3 mg in 24 hours and 4 mg in 7 days. Prior to use, the spray should be primed with 4 pumps. The applicator should be discarded with any remaining drug after 8 hours. Should not be used for chronic daily administration.
Bupap, Tencon, Allzital (butalbital/APAP)	Tablet, capsule	Oral	One to two tablets or capsules every 4 hours.	Maximum 6 tablets or capsule
Fioricet, Vtol LQ (butalbital/caffeine/APAP)	Capsule, oral solution	Oral	Capsule: 1 or 2 two tablets every 4 hours. Oral solution: 1 or 2 tablespoons (15 or 30 mL) every 4 hours	Capsule: Maximum 6 tablets Oral solution: Maximum 6 tablespoons.
Fiorinal (butalbital/caffeine/ASA)	Tablet	Oral	One to two tablets every 4 hours.	Maximum 6 tablets.
Reyvow (lasmiditan)	Tablet	Oral	One tablet (50 mg, 100 mg, or 200 mg), as needed.	Maximum 1 tablet every 24 hours. Maximum 4 tablets in 30 days. Should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery. A second dose has not been shown to be effective for the same migraine attack.

Abbreviations: APAP = acetaminophen, ASA = aspirin

- Ergotamine tartrate
  - Should only be used for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties.
  - Should not be used for daily, chronic administration.
  - Overdosage
    - Patients should be advised to report any of the following immediately: numbness or tingling in the fingers or toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, vomiting, cyanosis of the extremities.

- Fiorinal, Fioricet (butalbital component)
  - May impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery
  - Concomitant use of alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.
  - Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.
  - Acute barbiturate poisoning causing drowsiness, confusion, and coma, respiratory depression, hypotension, hypovolemic shock.

- Reyvow
  - .Drug abuse and dependence: lasmitidan is a schedule V controlled substance; Phase 2 and 3 studies have demonstrated the potential to produce euphoria or hallucinations at therapeutic doses (about 1% of patients). Patients should be evaluated/observed for risk of drug abuse/misuse.

- See the current prescribing information for full details

CONCLUSION

- Ergot alkaloids, butalbital combinations and lasmiditan are 3 classes of analgesics commonly used to treat primary headache types including migraine and TTH. Use with ergot alkaloids and butalbital combinations should be limited to treating 2 to 3 headache days a week in order to minimize the risk of MOH.
- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies. Ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism but may be enhanced with caffeine. DHE nasal spray administration bypasses this and can deliver adequate plasma concentrations for effective treatment. For moderate to severe attacks, AHS guidelines recommend the use of non-oral formulations such as DHE IN if severe nausea or vomiting are associated with a migraine attack.
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, NSAIDs, APAP), and moderate to severe attacks are treated more migraine specific agents.
- Butalbital combinations are FDA-approved for muscular headache or TTH and use has been studied in adults and pediatric patients aged ≥ 12 years. All butalbital-containing agents are paired with APAP or ASA with or without caffeine. NSAIDs and ASA are widely prescribed as acute medications for migraine. NSAIDs are still the mainstay for acute TTH, because they are less likely to lead to MOH compared to butalbital or APAP. The use of butalbital for patients with TTH may be considered in situations where NSAIDs are relatively contraindicated (eg, late in pregnancy) or when simple analgesics with caffeine are ineffective. Combination agents of butalbital with APAP may be used when other analgesics are contraindicated due to ulcers or severe renal failure. Butalbital with ASA may be used in hepatic failure.
  - The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, ASA) followed by combination analgesics containing caffeine plus a simple analgesic. Guidelines for the treatment of TTH recommends against the use of combination products with codeine or butalbital due to the increased risk of developing MOH.
- The ergot alkaloids include formulations of ergotamine tartrate (available orally and rectally) and DHE (available intranasally and as injectable forms). With the advent of triptans, the use of oral ergot alkaloids have been largely displaced in migraine therapy, as they have been found to be less effective than triptans in head-to-head trials and often reported to have poor tolerability with nausea frequently reported. The ergot alkaloids are associated with increased risk

of vascular events, so use in patients with peripheral vascular disease, coronary heart disease, or other certain CV indications are contraindicated.

- Lasmiditan is a first-in class selective 5HT-1F receptor agonist that has demonstrated efficacy in achieving pain freedom and MBS freedom 2 hours after treatment in clinical trials. According to guidelines from the AHS, lasmiditan may play a role in patients who have failed, have contraindications to, or who cannot tolerate triptans.
  - Lasmiditan is associated with driving impairment, and an inability to self-assess the degree of impairment, which is a limitation to use. Patients should be advised not to operate a vehicle (or other machinery) for at least 8 hours after administration. Common AEs include dizziness, fatigue, paresthesia, and sedation.
- Guidelines for acute migraine recommend lasmiditan as a specific therapy option on par with the CGRP inhibitors; however, safety issues may limit use. Ergot alkaloids have smaller place-in-therapy and based on efficacy and safety outcomes, European guidelines recommend avoiding ergotamine's, while US and Canada guidelines cite it as an option for acute migraine use.

REFERENCES

- Allzital [package insert], Canton, MS: Larken Laboratories, Inc.; September 2020.
- American Headache Society (AHS). The American headache society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019 Jan;59(1):1-18.
- Atlas S, Touchette D, Agboola F, et al. Acute treatments for migraine: Effectiveness and value. Institute for Clinical and Economic Review. Acute treatments for migraine. January 10, 2020. https://icer.org/wp-content/uploads/2020/10/ICER_Acute-Migraine_Final-Evidence-Report_Policy-Recommendations_022520-1.pdf. Accessed May 3, 2021.
- Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J. EFNS guideline on the treatment of tension type headache report of an EFNS task force. *Eur J Neurol*. 2010; 17(11): 1318-1325.
- Brandes JL, Klise S, Krege JH, et al. Interim results of a prospective, randomized, open-label, Phase 3 study of the long-term safety and efficacy of lasmiditan for acute treatment of migraine (the GLADIATOR study). *Cephalalgia*. 2019;39(11):1343-1357.
- Bupap [package insert], Bridgewater, NJ: Bausch Heath US, LLC; April 2020.
- Cafergot [package insert], Princeton, NJ: Sandoz Inc.; May 2018.
- Christie S, Gobel, H, Mateos V, Allen C, Vrijens F, Shivaprakash M: for the Rizatriptan-ergotamine/caffeine Preference Study Group. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol.* 2003;49(1):20-29.
- Cutrer FM. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. UpToDate website. Updated November 5, 2020. http://www.uptodate.com/. Accessed April 20, 2021.
- Derosier F, Sheftell F, Silberstein S, et al. sumatriptan-naproxen and butalbital: a double-blind, placebo controlled crossover study. *Headache*. 2012;52(4):530-543.
- Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. *The Cochrane Database Sys Rev*. 2012(2):CD009663.
- Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. *The Cochrane Database Sys Rev.* 2012(2):CD009665.
- Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TG. Efficacy, tolerability, and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicenter, Rrandomized, touble-blind, placebo-controlled comparison. *Eur Neurol*. 2002;47:99–107.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 20, 2021.
- Ergomar sublingual [package insert], Deerfield, IL: TerSera Therapeutics, LLC; February 2020.
- Evers S, Aphra J, Freese A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. *Eur J Neurol*. 2009;16(9):968-81.
- FDA Guidance for Industry. Migraine: developing drugs for acute treatment. February 2018. https://www.fda.gov/media/89829/download. Accessed April 21, 2021.
- Fioricet [package insert], Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; January 2021.
- Fiorinal [package insert], Madison, NJ: Allergan USA, Inc; June 2018.
- Garza I and Schwedt TJ. Medication overuse headache: Etiology, clinical features, and diagnosis. UpToDate website. Updated August 13, 2019. http://www.uptodate.com/. Accessed April 21, 2021.
- Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142(7):1894-1904.
- Halker Singh RB, VanderPlum JH, Morrow AS, et al. Acute treatments for episodic migraine. Comparative effectiveness review No. 239. AHRQ Publication No. 21-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; December 2020.
- Hou M, Xing H, Li C, et al. Short-term efficacy and safety of lasmiditan, a novel 5-HT 1F receptor agonist, for the acute treatment of migraine: a systematic review and meta-analysis. *J Headache Pain*. 2020;21(1):66-78.
- International Headache Society (IHS). IHS Classification ICHD-3. 2018. https://www.ichd-3.org/. Accessed April 20, 2021.
- Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB; for the COL MIG-301 Study Group. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology*. 2018;91(24):e2222-e2232.
- Láinez MJA, Galván J, Heras J, Vila C. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy. *Eur J Neurol.* 2007;14(3):269-275.
- Loo LS, Plato BM, Turner IM, et al. Effect of a rescue or recurrence dose of lasmiditan on efficacy and safety in the acute treatment of migraine: findings from the phase 3 trials (SAMURAI and SPARTAN). *BMC Neurol*. 2019;19(1):191.

- Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- Menshawy A, Ahmed H, Ismail, A. Intranasal sumatriptan for acute migraine attacks: a systematic review and meta-analysis. *Neurol Sci*. 2018; 39: 31-44.
- Migergot [package insert], South Plainfield, NJ: Cosette Pharmaceuticals, Inc.; July 2019.
- Migranal [package insert], Bridgewater, NJ: Bausch Heath US, LLC; July 2019.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 20, 2021.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: acute treatment of migraine in children and adolescents: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019;93(11):487-499.
- Reddy DS. The pathophysiological and pharmacological basis of current drug treatment of migraine headache. *Expert Rev Clin Pharmacol*. 2013;6(3):271-288.
- Reyvow [package insert], Indianapolis, IN: Eli Lilly and Company; January 2021.
- Silberstein SD and McCrory DC. Butalbital: history, pharmacology, and efficacy. *Headache*. 2001;41:953-967.
- Silberstein SD and McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache*. 2003;43(2):144-166.
- Smith JH. Acute treatment of migraine in adults. UpToDate website. Updated March 29, 2021. http://www.uptodate.com/. Accessed April 21, 2021.
- Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European Headache Federation and lifting the burden: the global campaign against headache. *J Headache Pain*. 2019;20(1):57-109.
- Taylor FR. Tension-type headache in adults: Acute treatment. . UpToDate website. Updated November 10, 2020[b]. http://www.uptodate.com/. Accessed April 21, 2021.
- Taylor FR. Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis. UpToDate website. Updated November 10, 2020[a]. http://www.uptodate.com/. Accessed April 21, 2021.
- Tencon [package insert], San Juan, PR: International ethical labs; July 2017.
- The Multinational Oral Sumatriptan and Caferget Comparative Study Group. A randomized double-blind comparison of sumatriptan and cafergot in the acute treatment of migraine. *Eur Neurol*.1991;31:314–322.
- Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. *Cephalalgia*. 2017;37(10):965-978.
- Touchon J, Bertin L, Pilgrim AJ, Ashford E, Bes A. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology*. 1996;47(2):361-365.
- Vtol LQ [package insert], Forth Worth, TX: Monarch PCM, LLC; August 2019.
- Worthington I, Pringsheim T, Gawel MJ, et al. Canadian Headache Society guideline: acute drug therapy for migraine headache. *Can J Neurol Sci.* 2013; 40(5 Suppl 3): S1-S80.
- Yang G, Sun Y, Gao B, Wang Z, Chen Z, Wang Z. Lasmiditan for acute treatment of migraine in adults: a systematic review and meta-analysis of randomized controlled trials. *CNS Drugs*. 2020;34(10):1015-1024.

Publication Date: May 28, 2021

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)

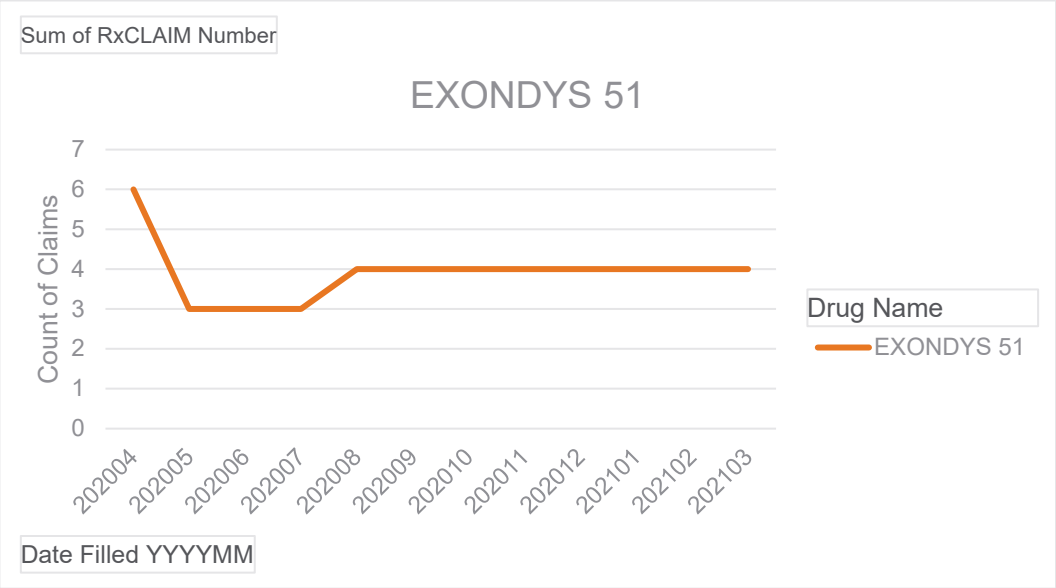
Nevada Medicaid

Duchenne Muscular Dystrophy Agents

Fee for Service

April 1, 2020 – March 31, 2021

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
EXONDYS 51	2	47	1,316	2,440



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

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):

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

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

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

3. Prior Authorization Guidelines

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

   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 a fatal, X-linked neuromuscular disorder caused by *DMD* gene mutations that result in the absence or near-absence of functional dystrophin protein in muscle cells and progressive loss of skeletal and cardiac function (*Institute for Clinical and Economic Review [ICER] 2019*).
  - DMD is the most common pediatric muscular dystrophy, with an incidence of about 400 to 600 cases per year and a prevalence of approximately 6000 males in the US (*ICER 2019*).
- Diagnosis of DMD typically occurs in early childhood, with symptoms beginning around 3 to 5 years of age. Early symptoms include muscle weakness, clumsiness, difficulty with rising from a squatted position (Gower's sign), and difficulty going up and down stairs (*ICER 2019*).
  - DMD patients may also have developmental delay, behavioral issues, impaired growth, delayed puberty, adrenal insufficiency, and gastrointestinal complications (eg, dysphagia and gastroparesis) (*ICER 2019*).
  - Osteoporosis with resultant fractures may occur from the disease itself and as an AE of glucocorticoid therapy (*ICER 2019*).
  - Loss of ambulation typically occurs by 12 years of age. Fatal respiratory or cardiac complications frequently develop in the second or third decade of life, and many deaths occur in the setting of an acute infection (*Food and Drug Administration [FDA] Vyondys 53 summary review 2020, ICER 2019*).
- Dystrophin forms an important part of the glycoprotein complex, strengthening and connecting muscle fibers in skeletal and cardiac muscle. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue (*ICER 2019*).
- DMD may be caused by more than 2000 mutations in the *DMD* gene that result in loss of expression or expression of nonfunctional dystrophin protein. An estimated 70% of DMD patients have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing. Disease severity appears to vary by mutation, resulting in a heterogeneous population with differing rates of progression (*ICER 2019*).
- Becker muscular dystrophy (BMD) has a similar presentation to DMD, but typically has a later onset (5 to 60 years of age) and a milder clinical course. BMD patients typically remain ambulatory into adult life and survive beyond the age of 30 years (*Darras 2020*).

Table 1. Clinical features of DMD vs BMD (*Darras 2020*)

	Duchenne muscular dystrophy	Becker muscular dystrophy
Clinical course	Severe	Mild
Age of onset	3 to 5 years	5 to 60 years
Loss of ambulation	Early teens	Adulthood
Common *DMD* gene mutations	Out-of-frame exon deletion/ duplication, nonsense mutation	In-frame exon deletion/ duplication, missense mutation
Dystrophin expression by immunohistochemistry	Absent	Reduced
Dystrophin expression by western blot	< 5% of normal	> 20% of normal

- There are currently no therapies available to cure DMD or halt disease progression (*Messina and Vita 2018*).
- Corticosteroids are the mainstay of pharmacologic therapy for DMD. Early initiation of corticosteroids has been associated with prolonged ambulation, decreased contractures and deformities, and prolonged function and participation in activities of daily living. Steroids are usually begun early in the disease course, prior to substantial physical decline. AEs of corticosteroids include weight gain, hirsutism, decreased bone density with increased risk of fracture, and cataracts (*ICER 2019, Messina and Vita 2018*).
  - In 2017, Emflaza (deflazacort) was the first corticosteroid FDA approved specifically for DMD. In clinical trials of DMD patients, treatment with deflazacort offered similar benefits to prednisone and was associated with less weight gain; however, deflazacort may be associated with an increased risk of cataracts compared with prednisone (*ICER 2019*).

- Many patients with DMD carry mutations in the *DMD* gene that cause misalignments in the transcription reading frame, leading to nonfunctional or absent dystrophin. As part of RNA synthesis, exons are connected to generate mRNA that encodes dystrophin, and mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted (*ICER 2019*).
  - Exon-skipping therapies are antisense oligonucleotides that prevent mutated exons from being transcribed, allowing for downstream exons to be transcribed in the correct reading frame. The remaining exons form a shortened mRNA that encodes a truncated, partially functional dystrophin protein. Animal models and anecdotal data suggest that restoration of small amounts of dystrophin (between 2 to 4% of normal) may be beneficial in slowing DMD progression; however, clinical correlation has yet to be established (*ICER 2019*).
- There are 4 exon-skipping therapies with FDA approval for DMD. Each therapy received biomarker-based accelerated approval based on increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies (*FDA Amondys 45 summary review 2021*).
  - Exondys 51 (eteplirsen) was the first exon-skipping therapy to receive FDA approval for DMD in 2016. It remains the only therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population) (*FDA Exondys 51 summary review 2016*).
    - Prior to approval, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against the efficacy of eteplirsen for DMD based on a single historically-controlled study and against the availability of substantial evidence from adequate and well controlled studies that eteplirsen induced dystrophin production to a level that was reasonably likely to predict clinical benefit (*FDA Exondys 51 summary review 2016*).
    - An appeal of the decision to approve eteplirsen convened the Agency Scientific Dispute Process Review Board, whose Chair ultimately agreed with the conclusions of the Director of the Office of Drug Evaluation I (ODE-1) that the overall evidence derived from the limited clinical development program did not support that the levels of dystrophin produced by eteplirsen were reasonably likely to provide clinical benefit (*FDA Vyondys 53 clinical review 2020*).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) were approved in 2019 and 2020, respectively, for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population) (*FDA Viltepso clinical review 2020, FDA Vyondys 53 summary review 2020*).
    - Golodirsen was initially issued a complete response letter issued based on the determination that the small, unverified benefit with golodirsen did not outweigh the risks for renal toxicity and serious infections related to drug delivery. FDA approval of golodirsen was granted upon appeal (*FDA Vyondys 53 clinical review 2020*).
  - Amondys 45 (casimersen) was approved in 2021 as the only therapy for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population) (*FDA Amondys 45 summary review 2021*).
- Ataluren is an oral therapy that promotes ribosomal read-through of nonsense (stop) mutations, which are present in 10 to 15% of patients with DMD. Although not approved by the FDA, ataluren is available to patients in 23 countries through either expanded access programs or commercial sales (*Darras 2021*).
- Clinical trials for investigational DMD therapies are ongoing, including gene transfer by intravascular administration of recombinant adeno-associated viral vectors that carry microdystrophin or minidystrophin genes (*Darras 2021*).
- Medispan classes: Neuromuscular agents, muscular dystrophy agents; Corticosteroids, glucocorticosteroids

Table 2. Medications Included Within Class Review

Drug	Generic Availability
Amondys 45 (casimersen)	-
Emflaza (deflazacort)	-
Exondys 51 (eteplirsen)	-
Vyondys 53 (golodirsen)	-
Viltepso (viltolarsen)	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 3. FDA-Approved Indications

Indication	Amondys 45 (casimersen)	Emflaza (deflazacort)	Exondys 51 (eteplirsen)	Vyondys 53 (golodirsen)	Viltepso (viltolarsen)
Treatment of DMD in patients ≥ 2 years of age		✔			
Treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping	✔				
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				✔	✔

(*Prescribing information: Amondys 45 2021, Emflaza 2021, Exondys 51 2020, Viltepso 2021, Vyondys 53 2021*)

- 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

Corticosteroids (deflazacort)

- There is considerable experience with the use of Emflaza (deflazacort) and other corticosteroids for the management of patients with DMD. Several observational studies have assessed the long-term effects of corticosteroid use on muscle strength, ambulation, weight gain, and other outcomes. Overall, these studies concluded that patients taking steroids performed better on functional outcome testing and experienced prolonged ambulation vs untreated patients (*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 moderate quality evidence supporting 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 was no evidence other than from non-randomized trials to establish the effect of corticosteroids on prolongation of ambulation (*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, 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 (*FDA Emflaza summary review 2017).*

- 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 loss of ambulation, 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 loss of ambulation was significantly longer in patients treated with 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*).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- 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 (*Exondys 51 prescribing information 2020*).
  - Study 201 was a 24-week, Phase 2b, DB, PC, RCT (N = 12) that evaluated the surrogate outcome of dystrophin production and the clinical efficacy outcome of 6-minute walk test (6MWT) distance in boys aged 7 to 13 years of age that were stable on corticosteroid treatment for at least 6 months. Patients were randomized to weekly intravenous (IV) infusions of eteplirsen 30 or 50 mg/kg/wk or placebo for 24 weeks (n = 4 for each group). Patients in the placebo group were switched to 30 or 50 mg/kg of eteplirsen (n = 2 for each group) at week 25. Study 202 was a 212-week, 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 meters, p ≤ 0.001) vs placebo (*Mendell et al 2013*).
    - The mean dystrophin protein expression after 180 weeks of treatment with eteplirsen was 0.93% of the normal dystrophin level in healthy subjects (*Exondys 51 prescribing information 2020*).
      - 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 (*FDA Exondys 51 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) (*FDA Exondys 51 summary review 2016*).
    - Long-term results from Study 201/202 demonstrated attenuation in pulmonary function decline (p < 0.001) and fewer patients with loss of ambulation at 4 years (17% vs 88%; p = 0.007) with eteplirsen (n = 12) compared with an untreated natural history control group (n = 20) of DMD patients amenable to exon 51 skipping from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) matched for baseline characteristics (*McDonald et al 2020*).
  - The Phase 3, OL PROMOVI trial (Study 301) was designed to evaluate the primary endpoint of 6MWT distance in 79 DMD patients treated with eteplirsen for 96 weeks compared with 30 patients in an untreated control group of DMD patients with mutations that were not amenable to exon 51 skipping (*ClinicalTrials.gov Web site*).
    - Accelerated approval of eteplirsen was based on western blot analyses of 13 patients enrolled in PROMOVI, which was ongoing at the time of FDA review. Among the 12 patients with evaluable results, mean dystrophin expression increased from 0.157% of normal at baseline to 0.440% of normal at Week 48 (mean change from baseline, 0.283%; p = 0.008). Overall, 8 (67%) patients experienced a change in dystrophin of ≤ 0.25%; only 1 patient (8%) experienced an increase > 1% of normal (*FDA Exondys 51 medical review 2016*).
    - The primary efficacy analysis was performed in all patients with a baseline 6MWT distance of 300 to 450 meters and ≥ 1 post-baseline functional assessment. The mean change from baseline to week 96 in 6MWT distance was −117.91 meters in 65 evaluable patients treated with eteplirsen and −133.56 meters in 9 evaluable patients in the untreated control group. The proportion of patients with loss of ambulation at week 96 was 17.9% in 67 evaluable

eteplirsen-treated patients, compared to 5.0% in 20 evaluable patients in the untreated control group (*ClinicalTrials.gov Web site*).
    - According to a poster presented at the World Muscle Society Virtual Congress, PROMOVI included a flawed comparison of eteplirsen-treated patients with a mismatched control arm that consisted entirely of patients with mutations not amenable to exon 51 skipping. Inadequate choice of control group became clear after study initiation, as emerging natural history data demonstrated patients with different mutations have different disease trajectories. Additionally, the control arm did not retain enough patients (15 of 30 completed the study) to allow for statistically and clinically meaningful comparisons (*McDonald et al 2020*).
  - The confirmatory study for eteplirsen (MIS51ON; NCT03992430) was initiated in 2020 with an estimated completion date in 2026. The randomized, DB phase will evaluate the safety and efficacy of a high dose of eteplirsen compared to the FDA-approved dose of 30 mg/kg IV weekly (*ClinicalTrials.gov Web site*).
- Vyondys 53 (golodirsen) was evaluated in SKIP-NMD, a 2-part, Phase 1/2 trial that enrolled ambulatory boys aged 6 to 15 years with DMD caused by out-of-frame deletions amenable to exon 53 skipping. Part 1 (n = 12) was a 12-week, Phase 1, DB, PC, dose-escalation RCT that established the safety of golodirsen. Part 2 of SKIP-NMD was a 168-week, Phase 2, OL evaluation of efficacy with golodirsen (*Frank et al 2020*).
  - Accelerated approval of golodirsen was based on the surrogate endpoint of dystrophin expression assessed by western blot. At interim analysis (n = 25), mean dystrophin expression increased from 0.095% of normal at baseline to 1.019% of normal at Week 48 (mean change from baseline, 0.924%; p < 0.001) (*Frank et al 2020*).
  - For the primary efficacy outcome of 6MWT distance, the mean change from baseline to 144 weeks was −99.0 meters in 22 evaluable patients treated with golodirsen and −160.8 meters in 6 evaluable patients who were not amenable to exon 53 skipping and did not receive treatment (*ClinicalTrials.gov Web site*).
  - The confirmatory study for golodirsen (ESSENCE; NCT02500381) is an ongoing Phase 3 trial with a 96-week, DB, PC phase followed by a 48-week OL phase with an estimated completion date in 2023. The primary endpoint will be the change in 6MWT distance from baseline to Week 96 (*ClinicalTrials.gov Web site*).
- Viltepso (viltolarsen) was evaluated in a 2-part, Phase 2, MC trial that enrolled 16 ambulatory boys aged 4 to 9 years with DMD amenable to exon 53 skipping. Two doses of viltolarsen (40 mg/kg/week [unapproved dose] and 80 mg/kg/week [approved dose]) were evaluated as add-on therapy to a stable dose of glucocorticoids. Part 1 was a 4-week, randomized, DB, PC period that established the safety of viltolarsen. Part 2 was a 20-week, OL treatment period that evaluated the efficacy and safety of low-dose and high-dose viltolarsen (*Clemens et al 2020*).
  - Accelerated approval of viltolarsen was based on an increase in dystrophin from 0.3% of normal at baseline to 5.7% of normal at week 25 with low-dose viltolarsen (mean change, 5.4%; p < 0.001), and from 0.6% of normal at baseline to 5.9% of normal at week 25 with high-dose viltolarsen (mean change, 5.3%; p = 0.01). Assessment of functional outcomes demonstrated improvement or stabilization of motor function with viltolarsen (n = 16) compared to an external natural history control group (n = 65) from the CINRG DNHS matched for age and treatment (*Clemens et al 2020*).
  - The confirmatory RACER53 trial (NCT04060199) for viltolarsen is an ongoing Phase 3, DB, PC, MC, RCT with an estimated completion date in 2024. The primary outcome will be the change from baseline to Week 48 in the time to stand test. Other functional outcomes include the time to run/walk 10 meters test, 6MWT, North Star Ambulatory Assessment (NSAA), and time to climb 4 steps test (*ClinicalTrials.gov Web site*).
- Amondys 45 (casimersen) was evaluated in the ongoing 96-week, Phase 3, randomized, DB, PC, MC ESSENCE trial that will serve as the confirmatory trial for both casimersen and golodirsen (*FDA Amondys 45 clinical review 2021*).
  - The casimersen arm of the ESSENCE study enrolled boys 7 to 13 years of age with a clinical diagnosis of DMD and a documented mutation amenable to exon 45 skipping. Key inclusion criteria included a mean 6MWT distance ≥ 300 and ≤ 450 meters, stable pulmonary and cardiac function, and stable corticosteroid therapy for ≥ 24 weeks (*FDA Amondys 45 clinical review 2021*).
  - Accelerated approval of casimersen was based on an interim analysis of the ESSENCE trial in 43 patients randomized to receive casimersen (n = 27) or placebo (n = 16) once weekly via IV infusion for 48 weeks. Mean dystrophin protein expression increased from 0.93% of normal levels at baseline to 1.74% at week 48 in the casimersen group (mean change from baseline, 0.81%; p < 0.001), as compared to 0.54% of normal at baseline to 0.76% at week 48 in the placebo group (mean change from baseline, 0.22%; p = 0.089). The between-group difference in dystrophin expression with casimersen vs placebo was 0.59% (p = 0.004) (*FDA Amondys 45 clinical review 2021*).

Table 4. FDA-approved exon-skipping therapies for DMD (*ClinicalTrials.gov Web site, Exondys 51 prescribing information 2020, FDA Amondys 45 clinical review 2021, ICER 2019, Viltepso prescribing information 2021, Vyondys 53 prescribing information 2021*)

Exon skipped	Amenable DMD Population	Drug	Manufacturer	Accelerated Approval	Dystrophin*	Confirmatory trial (Estimated completion date)
45	8%	**Amondys 45** (casimersen)	Sarepta	2021	0.81%	ESSENCE (2023)
51	13%	**Exondys 51** (eteplirsen)		2016	0.28%	MIS51ON (2026)
53	9%	**Vyondys 53** (golodirsen)		2019	0.92%	ESSENCE (2023)
		Viltepso (viltolarsen)	NS Pharma	2020	5.3%†	RACER53 (2024)

* Mean change from baseline in dystrophin measured by western blot as reported in the prescribing information
† Differences in the western blot assay methodology may prevent meaningful comparisons across studies

CLINICAL GUIDELINES

- **DMD Care Considerations Working Group: Diagnosis and management of DMD, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management** (*Birnkrant et al 2018*)
  - The DMD Care Considerations Working Group was supported by the CDC with involvement of the TREAT-NMD network for neuromuscular diseases, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy.
    - The guidance was not conventionally evidence based, as few large-scale RCTs have been completed for DMD, with the exception of corticosteroid studies.
    - No recommendations were provided to inform the place in therapy for eteplirsen, golodirsen, viltolarsen, or casimersen.
  - Consistent and reproducible clinical assessments of neuromuscular function performed by trained practitioners underpin the management of DMD.
    - The NSAA and timed function tests should be assessed every 6 months. They have high validity and reliability, as well as correlation between tests across time, minimum clinically important differences, and predictive capabilities regarding functional motor changes that are important in monitoring clinical progression and assessing new and emerging therapies.
    - Before 7 years of age, gains might occur in the 6MWT and timed function tests. After 7 years of age, a 6MWT distance < 325 meters and a mean linearized NSAA of 34 or less (raw score of 9) have been associated with greater functional decline in ambulation over the subsequent 12 months.
  - Physiotherapy and glucocorticoids are the mainstays of DMD treatment and should continue after loss of ambulation.
    - The benefits of long-term glucocorticoid therapy include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.
    - Although the benefits of glucocorticoid therapy are well established, uncertainty remains about which glucocorticoids are best and at what doses.
  - Although the DMD Care Considerations Working Group acknowledged the FDA approval of eteplirsen, no specific recommendations were provided.

- **American Academy of Neurology (AAN) − Practice guideline update summary: Corticosteroid treatment of DMD** (*Gloss et al 2016, reaffirmed 2019*)
  - The AAN recommendations are focused on corticosteroid therapy; no recommendations are provided regarding exon-skipping therapies.
  - In children with DMD, prednisone should be offered to improve strength (Level B) and pulmonary function (Level B).
  - Prednisone may be offered to improve timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C).

- Deflazacort may be offered to improve strength and timed motor function and delay age at loss of ambulation by 1.4 to 2.5 years (Level C). Deflazacort may be offered to improve pulmonary function, reduce the need for scoliosis surgery, delay cardiomyopathy onset, and increase survival at 5 to 15 years of follow-up (Level C for each).
- Deflazacort and prednisone may be equivalent in improving motor function (Level C).
- Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C).
- Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C).

SAFETY SUMMARY

Corticosteroids (deflazacort)

- Deflazacort is contraindicated in patients with known hypersensitivity to deflazacort or to any of the inactive ingredients.
- Warnings and precautions for 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%).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- There are no labeled contraindications to any of the exon-skipping therapies.
- Eteplirsen and golodirsen have a labeled warning for hypersensitivity reactions.
- Casimersen, golodirsen, and viltolarsen have warnings for kidney toxicity.
  - Although kidney toxicity was not reported in clinical trials with casimersen, golodirsen, or viltolarsen, it was observed in animal studies with these agents and in human studies with other antisense oligonucleotides.
- The most common AEs with exon-skipping therapies included:
  - Casimersen (incidence ≥ 20% and ≥ 5% higher than placebo): Upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain.
  - Eteplirsen (incidence ≥ 35% and higher than placebo): Balance disorder and vomiting.
  - Golodirsen (incidence ≥ 20% and higher than placebo): Headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.
  - Viltolarsen (incidence ≥ 15%): Upper respiratory tract infection, injection site reaction, cough, and pyrexia.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amondys 45 (casimersen)	Injection	IV infusion	Once weekly	Monitor renal function
Emflaza (deflazacort)	Tablets, suspension	Oral	Once daily	
Exondys 51 (eteplirsen)	Injection	IV infusion	Once weekly	
Vyondys 53 (golodirsen)	Injection	IV infusion	Once weekly	Monitor renal function
Viltepso (viltolarsen)	Injection	IV infusion	Once weekly	Monitor renal function

See the current prescribing information for full details

CONCLUSION

- DMD is a rare, genetic neuromuscular disease characterized by progressive loss of muscle function, resulting in early death due to respiratory or cardiac failure.
- No currently available therapies cure DMD or halt disease progression. Corticosteroids are the mainstay of pharmacologic therapy for DMD and may prolong ambulation and participation in activities of daily living.
- Emflaza (deflazacort) is the only corticosteroid indicated specifically for the treatment of DMD. Deflazacort is available as oral tablets or suspension and is administered once daily.
  - Other corticosteroids such as prednisone have been used off-label for decades to treat DMD. RCTs and clinical practice guidelines do not support the superiority of one corticosteroid over the others for DMD.
- The FDA granted biomarker-based accelerated approvals to 4 antisense oligonucleotides that demonstrated increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The exon-skipping therapies are administered once weekly via IV infusion.
  - Amondys 45 (casimersen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population).
  - Exondys 51 (eteplirsen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) are both indicated for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population).
- The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies, which are expected to conclude between 2023 and 2026.

REFERENCES

- Amondys 45 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc.; February 2021.
- Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C. Deflazacort in Duchenne dystrophy: study of long-term effect. *Muscle Nerve*. 1994;17(4):386-391.
- Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. *Am J Phys Med Rehabil*. 2005;84(11):843-850.
- Bello L, Gordish-Dressman H, Morgenroth LP, et al; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology*. 2015;85(12):1048-1055.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-267. doi: 10.1016/S1474-4422(18)30024-3.
- Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: A Phase 2 randomized clinical trial. *JAMA Neurol*. 2020;77(8):982-991. doi: 10.1001/jamaneurol.2020.1264.
- ClinicalTrials.gov Web site. https://clinicaltrials.gov. Accessed April 19, 2021.
- Darras BT. Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. UpToDate Web site. Updated July 24, 2020. https://www.uptodate.com/contents/duchenne-and-becker-muscular-dystrophy-clinical-features-and-diagnosis. Accessed April 19, 2021.
- Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. UpToDate Web site. Updated March 16, 2021. https://www.uptodate.com/contents/duchenne-and-becker-muscular-dystrophy-glucocorticoid-and-disease-modifying-treatment. Accessed April 19, 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 19, 2021.
- Emflaza [package insert], South Plainfield, NJ: PTC Therapeutics, Inc.; February 2021.
- Exondys 51 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc; July 2020.
- Food and Drug Administration (FDA). Amondys 45 clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213026Orig1s000SumR.pdf. March 18, 2021. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Amondys 45 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213026Orig1s000SumR.pdf. March 18, 2021. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Emflaza summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000SumR.pdf. March 9, 2017. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Exondys 51 medical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000MedR.pdf. October 26, 2016. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Exondys 51 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf. October 26, 2016. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Viltepso clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212154Orig1s000MedR.pdf. August 31, 2020. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Vyondys 53 clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000MedR.pdf. January 21, 2020. Accessed April 19, 2021.

- Food and Drug Administration (FDA). Vyondys 53 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000SumR.pdf. January 21, 2020. Accessed April 19, 2021.
- Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94(21):e2270-e2282. doi: 10.1212/WNL.0000000000009233.
- Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(5):465-472. doi: 10.1212/WNL.0000000000002337.
- Griggs RC, Miller JP, Greenberg CR, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurology*. 2016;87(20):2123-2131.
- Institute for Clinical and Economic Review (ICER). Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: Effectiveness and value: Final evidence report. https://icer-review.org/material/dmd-final-evidence-report/. August 15, 2019. Accessed April 19, 2021.
- Kim S, Campbell KA, Fox DJ, Matthews DJ, Valdez R; MD STARnet. Corticosteroid treatments in males with Duchenne muscular dystrophy: treatment duration and time to loss of ambulation. *J Child Neurol*. 2015;30(10):1275-1280.
- Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016;(5):CD003725.
- McDonald C, Shieh P, Abdel-Hamid HZ, et al. Open-label evaluation of eteplirsen in patients with Duchenne muscular dystrophy amenable to exon 51 skipping: PROMOVI trial. Poster presented at: World Muscle Society Virtual Congress; September 28-October 2, 2020.
- Mendell JR, Rodino-Klapac LR, Sahenk Z et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013 Nov;74(5):637-47.
- Messina S, Vita GL. Clinical management of Duchenne muscular dystrophy: the state of the art. *Neurol Sci*. 2018;39(11):1837-1845. doi: 10.1007/s10072-018-3555-3.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 19, 2021.
- Viltepso [package insert], Paramus, NJ: NS Pharma, Inc.; March 2021.
- Vyondys 53 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc.; February 2021.

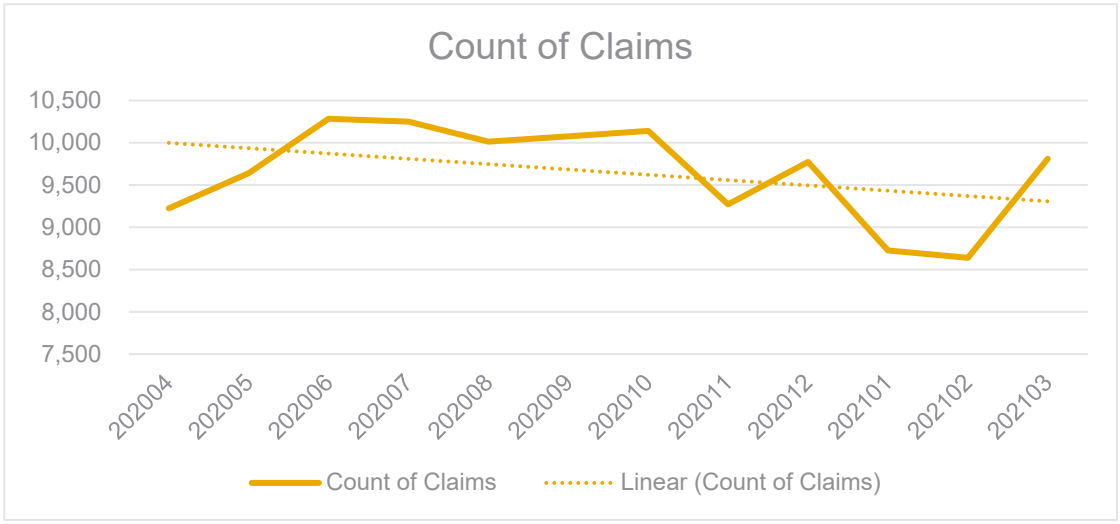
Publication Date: May 21, 2021

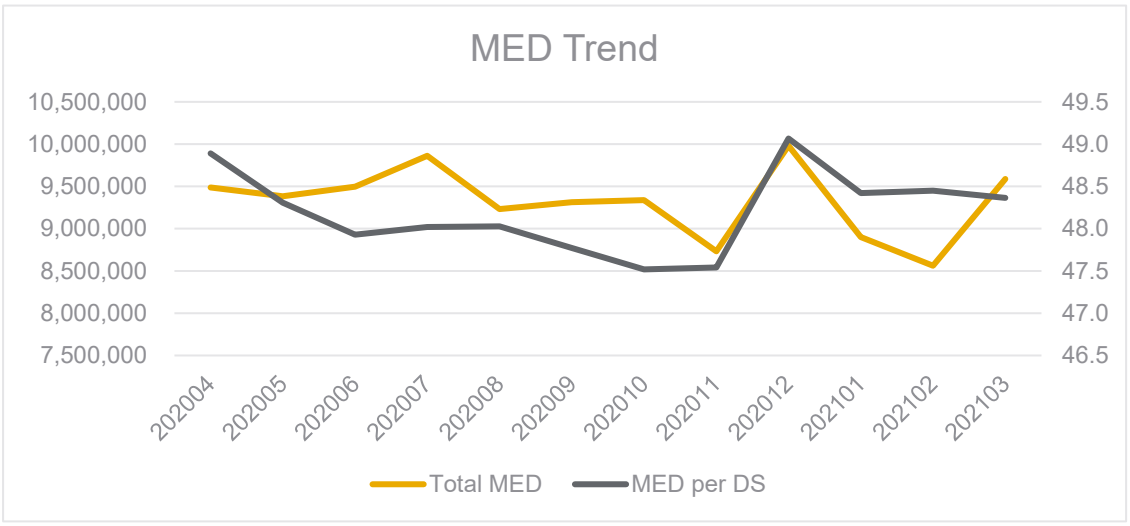
Board Requested Reports

Nevada Medicaid

Opioid Trends
Fee for Service
April 1, 2020 - March 31, 2021

Date Filled	Count of Claims	Days Supply	Count of Members	Total Qty	Total MED	MED per DS
202004	9,223	194,044	8,054	648,910	9,486,639	48.9
202005	9,640	194,219	8,424	648,123	9,382,113	48.3
202006	10,284	198,148	8,897	664,853	9,497,140	47.9
202007	10,249	205,347	8,817	691,340	9,860,818	48.0
202008	10,013	192,200	8,814	647,391	9,230,666	48.0
202009	10,076	194,960	8,836	659,402	9,313,441	47.8
202010	10,140	196,519	8,836	656,699	9,338,370	47.5
202011	9,271	183,657	8,225	614,818	8,731,258	47.5
202012	9,773	203,436	8,400	685,502	9,981,963	49.1
202101	8,726	183,800	7,860	622,999	8,899,862	48.4
202102	8,641	176,744	7,776	593,816	8,563,078	48.4
202103	9,810	198,235	8,470	668,665	9,587,333	48.4





Nevada Medicaid

Opioid Trends - Top Ten Members
Fee for Service
January 1, 2021 - March 31, 2021

Member ID Encrypted	Count of Claims	Day Supply	Total Quantity	Total MED
33330458115	6	180	1,140	63,600
44448546720	7	210	1,590	62,100
77771952964	7	210	870	59,400
11110100737	9	264	1,440	52,200
55550656157	14	420	1,200	49,005
22222296971	8	120	1,830	48,600
49044066667	6	180	990	48,600
99990949361	5	109	1,100	48,450
44446597311	5	150	570	45,900
77771924497	6	180	630	43,200

Member ID Encrypted	Drug Label Name	Count of Claims	Day Supply	Total Quantity
11110100737	METHADONE TAB 10MG	3	84	720
	MORPHINE SUL TAB 100MG ER	3	96	360
	OXYCODONE TAB 30MG	3	84	360
11110100737 Total		**9**	**264**	**1,440**
22222296971	FENTANYL DIS 100MCG/H	3	45	30
	OXYCODONE TAB 10MG	5	75	1,800
22222296971 Total		**8**	**120**	**1,830**
33330458115	MORPHINE SUL TAB 100MG ER	3	90	420
	OXYCODONE TAB 20MG	3	90	720
33330458115 Total		**6**	**180**	**1,140**
44446597311	FENTANYL DIS 100MCG/H	2	60	30
	OXYCODONE TAB 30MG	3	90	540
44446597311 Total		**5**	**150**	**570**
44448546720	HYDROCO/APAP TAB 10-325MG	3	90	270
	OXYCODONE TAB 30MG	4	120	1,320
44448546720 Total		**7**	**210**	**1,590**
49044066667	MORPHINE SUL TAB 60MG ER	3	90	270
	OXYCODONE TAB 30MG	3	90	720
49044066667 Total		**6**	**180**	**990**
55550656157	OXYCODONE CON 100/5ML	3	90	180
	OXYCODONE TAB 30MG	4	120	600
	XTAMPZA ER CAP 13.5MG	3	90	180
	XTAMPZA ER CAP 36MG	4	120	240
55550656157 Total		**14**	**420**	**1,200**
77771924497	MORPHINE SUL TAB 100MG ER	3	90	270
	OXYCODONE TAB 30MG	3	90	360
77771924497 Total		**6**	**180**	**630**
77771952964	FENTANYL DIS 100MCG/H	2	60	60
	METHADONE TAB 10MG	3	90	450
	OXYCODONE TAB 30MG	2	60	360
77771952964 Total		**7**	**210**	**870**
99990949361	OXYCODONE TAB 20MG	1	6	70
	OXYCODONE TAB 30MG	4	103	1,030
99990949361 Total		**5**	**109**	**1,100**

Nevada Medicaid

Fee for Service - Opioid Trends - Top Ten Prescribers

By Morphine Equivalent Dose (MED)

Quarter filled	Prescriber ID	City	State	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2020 Q4	Pres 14	SPARKS	MD	- Anesthesiology	103	271	7,937	23,156	606,965	76.47	0.74
2020 Q4	Pres 17	LAS VEGAS	-	- Anesthesiology	196	349	9,239	31,159	535,341	57.94	0.30
2020 Q4	Pres 25	LAS VEGAS	-	- Orthopedic Surgery	169	325	9,446	32,380	483,674	51.20	0.30
2020 Q4	Pres 9	LAS VEGAS	PAC	- Physician Assistant	111	231	6,609	21,951	458,528	69.38	0.63
2020 Q4	Pres 36	LAS VEGAS	PAC	- Physician Assistant	168	291	7,991	27,082	450,869	56.42	0.34
2020 Q4	Pres 1	LAS VEGAS	MD	- Hospitalist	102	206	5,742	18,880	444,528	77.42	0.76
2020 Q4	Pres 9	LAS VEGAS	PAC	- Physician Assistant	107	237	6,969	21,064	430,086	61.71	0.58
2020 Q4	Pres 35	HENDERSON	MS	Physician Assistants & Advance	97	201	5,489	18,929	422,689	77.01	0.79
2020 Q4	Pres 30	MIAMI	MD	- Anesthesiology	152	313	9,222	31,424	420,235	45.57	0.30
2020 Q4	Pres 11	HENDERSON	PAC	- Physician Assistant	44	90	2,654	9,927	385,965	145.43	3.31
2021 Q1	Pres 1	LAS VEGAS	MD	- Hospitalist	147	293	8,149	26,675	577,665	70.89	0.48
2021 Q1	Pres 14	SPARKS	MD	- Anesthesiology	89	235	6,670	20,492	531,830	79.73	0.90
2021 Q1	Pres 9	LAS VEGAS	PAC	- Physician Assistant	114	261	7,547	25,600	520,738	69.00	0.61
2021 Q1	Pres 36	LAS VEGAS	PAC	- Physician Assistant	142	323	9,063	30,482	503,729	55.58	0.39
2021 Q1	Pres 16	SPARKS	DO	Allopathic & Osteopathic Physic	112	291	8,537	34,995	503,418	58.97	0.53
2021 Q1	Pres 17	LAS VEGAS	-	- Anesthesiology	156	331	8,584	28,449	466,023	54.29	0.35
2021 Q1	Pres 25	LAS VEGAS	-	- Orthopedic Surgery	162	339	9,633	33,289	463,006	48.06	0.30
2021 Q1	Pres 35	HENDERSON	MS	Physician Assistants & Advance	87	170	4,939	16,862	412,230	83.46	0.96
2021 Q1	Pres 2	LAS VEGAS	-	-	95	186	5,509	19,899	408,026	74.07	0.78
2021 Q1	Pres 11	HENDERSON	PAC	- Physician Assistant	41	95	2,796	10,676	403,635	144.36	3.52

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

Quarter filled	Prescriber ID	City	State	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2020 Q4	Pres 10	RENO	-	-	1	1	10	90	1,800	180.00	180.00
2020 Q4	Pres 27	HENDERSON	-	- Hematology/Oncology, Peds	1	3	90	360	16,200	180.00	180.00
2020 Q4	Pres 23	SOUTH LAKE	MD	- Emergency Medicine	1	1	12	4	2,160	180.00	180.00
2020 Q4	Pres 15	LAS VEGAS	MD	Allopathic & Osteopathic Physic	1	1	10	40	1,800	180.00	180.00
2020 Q4	Pres 31	HENDERSON	MD	- Internal Medicine	1	2	10	40	1,800	180.00	180.00
2020 Q4	Pres 21	HENDERSON	-	-	1	7	20	200	3,000	150.00	150.00
2020 Q4	Pres 28	SAN ANTONIO	NP	- Nurse Practitioner	1	1	3	14	420	140.00	140.00
2020 Q4	Pres 13	LAS VEGAS	MD	- Specialist	2	5	150	930	41,850	279.00	139.50
2020 Q4	Pres 26	0	-	- Hematology/Oncology, Peds	1	1	6	36	810	135.00	135.00
2020 Q4	Pres 7	RENO	MD	- Internal Medicine	1	1	30	180	4,050	135.00	135.00
2021 Q1	Pres 27	HENDERSON	-	- Hematology/Oncology, Peds	1	2	60	240	10,800	180.00	180.00
2021 Q1	Pres 18	LAS VEGAS	-	- Nurse Practitioner	1	2	60	240	10,800	180.00	180.00
2021 Q1	Pres 20	HENDERSON	MD	- Internal Medicine	1	1	3	24	540	180.00	180.00
2021 Q1	Pres 31	HENDERSON	MD	- Internal Medicine	1	1	8	30	1,350	168.75	168.75
2021 Q1	Pres 37	LAS VEGAS	MD	- Family Practice	1	1	5	30	675	135.00	135.00
2021 Q1	Pres 34	RENO	-	- Hematology/Oncology, Peds	1	3	90	540	12,150	135.00	135.00
2021 Q1	Pres 33	LAS VEGAS	MD	Allopathic & Osteopathic Physic	1	3	90	720	10,800	120.00	120.00
2021 Q1	Pres 32	ATLANTIC	MD	- Specialist	1	1	15	60	1,800	120.00	120.00
2021 Q1	Pres 12	PAHRUMP	MD	- Internal Medicine	1	3	90	360	10,800	120.00	120.00
2021 Q1	Pres 22	LAS VEGAS	MD	- Internal Medicine	1	1	20	80	2,400	120.00	120.00

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

October 1, 2020 - March 31, 2021

Top 10 Classes by Claim Count

2021 Q1

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,010	$2,782,581.05
SYMPATHOMIMETICS	17,148	$2,776,809.02
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,582	$210,926.07
OPIOID COMBINATIONS	14,485	$422,549.68
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	13,051	$328,832.95
CENTRAL MUSCLE RELAXANTS	12,928	$213,138.83
HMG COA REDUCTASE INHIBITORS	11,272	$156,104.57
DIBENZAPINES	9,997	$388,235.27
ANTIANXIETY AGENTS - MISC.	9,729	$147,221.71
OPIOID AGONISTS	9,634	$374,384.42

2020 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,054	$2,722,594.84
SYMPATHOMIMETICS	18,736	$2,808,552.94
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,432	$208,325.27
OPIOID COMBINATIONS	15,157	$430,875.86
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	13,115	$324,714.31
CENTRAL MUSCLE RELAXANTS	12,980	$224,421.72
HMG COA REDUCTASE INHIBITORS	11,274	$377,969.88
DIBENZAPINES	10,181	$374,212.04
OPIOID AGONISTS	9,817	$383,803.75
ANTIANXIETY AGENTS - MISC.	9,657	$148,992.06

Top 10 Classes by Amount Paid

2021 Q1

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	133	$14,856,720.46
ANTIRETROVIRALS	1,774	$4,149,649.60
SPINAL MUSCULAR ATROPHY AGENTS (SMA)	15	$3,306,133.29
INSULIN	4,813	$3,254,544.57
ANTIPSYCHOTICS - MISC.	3,177	$2,926,168.01
ANTICONVULSANTS - MISC.	27,010	$2,782,581.05
SYMPATHOMIMETICS	17,148	$2,776,809.02
BENZISOXAZOLES	5,843	$2,657,143.75
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	288	$2,112,511.84
ANTINEOPLASTIC ENZYME INHIBITORS	175	$2,032,524.70

2020 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	126	$14,139,357.89
ANTIRETROVIRALS	1,877	$4,198,446.86
INSULIN	4,811	$3,325,160.58
SYMPATHOMIMETICS	18,736	$2,808,552.94
ANTIPSYCHOTICS - MISC.	3,079	$2,744,616.60
ANTICONVULSANTS - MISC.	27,054	$2,722,594.84
BENZISOXAZOLES	5,992	$2,614,160.78
CYSTIC FIBROSIS AGENTS	228	$2,136,069.30
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	304	$1,993,065.59
ANTINEOPLASTIC ENZYME INHIBITORS	179	$1,963,280.25

cDUR Quarterly Report

Client(s): 'NVM'
Carrier ID: NVM
Account(s): All
Group(s): All
Primary Start Date: January 1, 2021
Primary End Date: March 31, 2021

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	625,595	137,716	22.0%
Rejected	520,581	174,167	33.5%
Reversed	108,863	34,697	31.9%
Total	***1,255,039***	***346,580***	***27.6%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
48,898	**$6,545,719**	**24,202**	**$8,638,931**	**73,100**	**$15,184,650**	**73,100**	**$15,184,650**

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)	40,793	31,304	76.7%	1,056	2.6%	8,433	20.7%
Drug-Drug Interaction (DDI-DTMS)	112,333	51,072	45.5%	53,664	47.8%	7,597	6.8%
Duplicate Therapy (DUPTHER)	102,898	44,475	43.2%	49,384	48.0%	9,039	8.8%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	23	9	39.1%	N/A	N/A	14	60.9%
Duplicate Rx (DUPRX)	90,121	10,851	12.0%	69,660	77.3%	9,610	10.7%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	2	1	50.0%	N/A	N/A	1	50.0%
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	7	4	57.1%	N/A	N/A	3	42.9%
Refill Too Soon	403	N/A	N/A	403	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	***346,580***	***137,716***	***39.7%***	***174,167***	***50.3%***	***34,697***	***10.0%***

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)	1,386	$1,516,794	1,889	$3,561,885	3,275	$5,078,679	3,275	$5,078,679
Drug-Drug Interaction (DDI-DTMS)	3,369	$229,702	3,900	$999,373	7,269	$1,229,075	7,269	$1,229,075
Duplicate Therapy (DUPTHER)	5,116	$1,052,058	9,389	$2,873,201	14,505	$3,925,260	14,505	$3,925,260
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duplicate Rx (DUPRX)	38,657	$3,709,740	8,914	$1,194,368	47,571	$4,904,108	47,571	$4,904,108
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)	N/A	N/A	46	$1,365	46	$1,365	46	$1,365
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	$148	N/A	N/A	2	$148	2	$148
Refill Too Soon	368	$37,276	64	$8,738	432	$46,014	432	$46,014
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	***48,898***	***$6,545,719***	***24,202***	***$8,638,931***	***73,100***	***$15,184,650***	***73,100***	***$15,184,650***

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

Fourth Quarter 2020 and First Quarter 2021

Q4 2020

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
CGM II	114	31	49	114	27.19%
Albuterol Initiative Part 1	156	18	124	156	11.54%
Albuterol Initiative Part 2	157	17	120	157	10.83%

Q1 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Montelukast utilizers less than 21 yrs without Asthma dx	27	3	24	27	11.11%
Q1.2 2021 Long term PPI use with duplicate PPIs	69	11	60	69	15.94%
Q1.3 2021 Long Term PPI	139	17	121	139	12.23%