Nevada Medicaid Drug Use Review Board Meeting

April 28, 2022

OPTUMRx®

Table of Contents

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 Publication:	March 22, 2022
Date of Revision:	March 23, 2022
Date and Time of Meeting:	April 28, 2022, at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR)
Place of Meeting:	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 maybe 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.
Webinar:	Microsoft Teams (See final agenda page for full link or employ the shortened link directly below) OR https://tinyurl.com/APR-DUR-2022
Audio Only:	(952) 222-7450
Event Number:	386 024 126#

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 email to (rxinfo@dhcfp.nv.gov). Written comments will not be read into the record, but written comments are encouraged to be accessible to screen readers. 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 will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record. **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 January 27, 2022.
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 Movement Disorder 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.

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

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

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Monoclonal Antibodies for the treatment of respiratory conditions.

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

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

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. Presentation of opioid criteria.
ii. Discussion by the Board and review of utilization data.
iii. 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 Q3 2021 and Q4 2021 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q4 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.)

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 will 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. Email 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 at 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 email.

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 in advance of the meeting, by email at rxinfo@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701.

Full Microsoft Teams link:

https://teams.microsoft.com/l/meetup-join/19%3ameeting_OGI4N2M5NTctMjRjNi00ZDYxLTkyM2QtZjQ3OTRmYjRkYzY4%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%222311bd22-e984-4bae-84b9-bedd149b3c85%22%7d

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 three minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each board member and a copy (electronic preferred) for the official record.

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

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair	Dave England, Pharm.D.
Netochi Adeolokun, Pharm.D., Vice Chair	Brian Le, DO
Mark Canty, MD	Michael Owens, MD
Crystal Castaneda, MD	Rebecca Sparks, PA-C
Jessica Cate, Pharm.D.	Jim Tran, Pharm.D.

Web References

Medicaid Services Manual (MSM) Chapter 1200:

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

Drug Use Review Board Bylaws:

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

Drug Use Review Board Meeting Material:

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

Social Security Act, 1927:

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

Meeting Minutes

Drug Use Review Board

Meeting Minutes

Date of Meeting: Thursday, January 27, 2022

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	It was announced the meeting is being recorded. Chairwoman Wheeler called the meeting to order at 1:06 p.m. on January 27, 2022. Chairwoman Wheeler took the roll. Present / Absent 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. ☒ ☐	**The DHCFP Staff Present were as follows:** Woodrum, Homa, Senior Deputy Attorney General Capurro, Antonina, Deputy Administrator Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist (SSPS) III Berntson, Kindra, SSPS II Alegria, Veronica, SSPS I Evins, Jaime, Supervisor Managed Care Contracts

Agenda Item	Record			Notes
	Brian Le, DO	☒	☐	Flowers, Ellen, Program Officer I **Managed Care Organization representatives present were as follows:** Eletreby, Iman, Pharm.D., Anthem Blue Cross Bitton, Ryan, Pharm.D., Health Plan of Nevada Tran, Jimmy, Pharm.D., Molina Healthcare Beranek, Tom, RPh, SilverSummit Health Plan **Gainwell Technologies Staff Present were as follows:** Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** LeCheminant, Jill, Pharm.D. Piccirilli, Annette Kiriakopoulos, Amanda, Pharm.D. **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
	Michael Owens, MD	☒	☐	
	Rebecca Sparks, PA-C	☒	☐	
	Jim Tran, Pharm.D.	☒	☐	
	A quorum was present.			

Agenda Item	Record	Notes
		attendee list's accuracy is not assured.
2. General Public Comment	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Mr. John Phoenix, an APRN from the Huntridge Family Clinic, regarding the lack of representation of the nursing profession in the Board. He commented that he would like to update the regulation to permit advanced practice providers and nursing providers to join the Board. Chairwoman Wheeler notified Mr. Phoenix that the first physician assistant was added to the Board, Rebecca Sparks. Comment was provided by Dr. Dana McSherry from Vanda Pharmaceuticals and noted that a written public comment was submitted. The submission was regarding the criteria for Hetlioz. Chairwoman Wheeler noted that written public comment was received. Comment was provided by Dr. Jonathan McKinnon regarding casimersen. He noted he supports criteria to use in ambulatory and non-ambulatory children with Duchenne Muscular Dystrophy. He stated that exon skipping therapy could slow disease progression and assist with other functions that do not relate to ambulation. Comment was provided by Dr. Charlie Lovan with Abbvie Pharmaceuticals stating that he was available for questions should they arise.	
3. Administrative		
a. **For Possible Action**: Review and Approve Meeting Minutes from October 26, 2021	No corrections were offered. Board Member Canty moved to approve the minutes as presented, and Board Member Adeolokun seconded the motion.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>A vote was taken, the results were as follows from members in attendance (in favor, against, and abstentions where applicable):

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Brian Le, DO</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Michael Owens, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Rebecca Sparks, PA-C</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jim Tran, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
<tr><td>b. Status Update by DHCFP</td><td>Chief David Olsen announced DHCFP is working to establish pharmacists as a new provider type. On January 13, 2022, the Nevada State Board of Pharmacy approved a protocol and regulation of Senate Bill 190. The Board of Pharmacy legislative council will review and revise the protocol. Senate Bill 325 requires a protocol for prescribing and ordering related lab tests for dispensing HIV treatment medications, PEP and PREP, which will be reviewed in March 2022. Due to required approvals and onboarding of a new pharmacy benefit manager (PBM), June 2022 is the earliest expected date for implementing the new provider type.

Chief Olsen reported Magellan Medicaid Administration (MMA) as the new PBM beginning July 1, 2022. After that date, Magellan will facilitate the Drug Use Review Board Meetings.

Chief Olsen stated that a public meeting would be held on January 28, 2022, at 1:00 p.m. to discuss public insurance. He referenced the DHCFP website for public notice details.</td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Mr. Antonio Gudino welcomed new Board Member Rebecca Sparks, PA-C. Rebecca works as a certified physician assistant in a local Community Health Center, where she provides medical care to the underinsured and underserved populations. She also provides services at a local acute care clinic. DHCFP has scheduled a public workshop on February 7, 2022, to discuss a proposed state plan amendment to enroll into the National Medicaid Pooling Initiative (NMPI) for supplemental rebate agreements. The NMPI is a multi-state Medicaid pharmaceutical purchasing pool that allows Nevada Medicaid to consolidate purchasing power to negotiate a lower price for prescription drugs. There are twelve states taking part in NMPI. The DHCFP website was referenced for additional public notice information regarding the workshop.	
4. Clinical Presentations		
a. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for CGRP Products		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was provided. No written comment was received.	
ii. Presentation of utilization and clinical information.	Dr. Jill LeCheminant reviewed the new agent Qulipta and discussed the consolidation of criteria. She discussed the efficacy of Qulipta and migraine-free days. She noted that the proposed criteria would be categorized by diagnosis. Dr. Iman Eletreby agreed with the proposed criteria.	

Agenda Item	Record	Notes
	Dr. Ryan Bitton agreed with the proposed criteria and noted an increase in utilization. Mr. Tom Beranek agreed with the proposed criteria.	
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 motioned to approve the criteria as presented. 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 ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Rebecca Sparks, PA-C ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
b. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Cystic Fibrosis Agents		

Agenda Item	Record	Notes
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Ms. Lisa Allen with Vertex Pharmaceuticals. She provided clinical information regarding the four available Cystic fibrosis transmembrane conductance regulator (CFTR) modulators. She noted the label updates and expansions to the available agents. Ms. Allen provided post-marketing data and warnings. She asked the Board to continue to provide access to the four CFTR agents based on indication and age. No written comment was received.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant presented information regarding an age update to Trikafta. She noted the previous use was for 12 years of age and older, and the new age is now six years of age and older. She requested the PA criteria be updated from specific age restrictions to age based on appropriate labeling to ensure timeliness for patient use. She provided updates to mutations in CFTR genes that are responsive to Trikafta. Utilization data is relatively steady, with a slight increase in Trikafta. Dr. Eletreby agreed with the proposed criteria and noted that Trikafta is the dominant agent with relatively low utilization. Dr. Bitton agreed with the proposed criteria and noted similar Trikafta utilization. Mr. Beranek agreed with the proposed criteria. He noted utilization of the class products.	
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 Le moved to approve the criteria as presented. 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. Dave England, Pharm.D. ☒ Yes ☐ No ☐ Abst. Brian Le, DO ☒ Yes ☐ No ☐ Abst. Michael Owens, MD ☒ Yes ☐ No ☐ Abst. Rebecca Sparks, PA-C ☒ Yes ☐ No ☐ Abst. Jim Tran, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
c. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Topical Immunomodulators.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was 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. LeCheminant discussed Opzelura topical use in atopic dermatitis. She noted efficacy in clinical trials for mild to moderate atopic dermatitis patients. Dr. Eletreby agreed with the proposed criteria and noted high utilization of Tacrolimus.	

Agenda Item	Record	Notes
	Dr. Bitton agreed with the proposed criteria but recommended the wording "topical prescription therapies" be updated for clarification. Mr. Beranek agreed with proposed criteria. He noted the utilization of Tacrolimus and Eucrisa.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. The Board discussed options to clarify the wording of the criteria.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member England moved to accept the proposed criteria with the phrase "topical prescription therapies" changed to "other topical prescription therapies." Board Member Adeolokun seconded the motion. A vote was held: Yes / No / Abst. Jennifer Wheeler, Pharm.D., Chair ☒ ☐ ☐ Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Rebecca Sparks, PA-C ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
d. **<u>For Possible Action</u>**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Cabenuva.		

Agenda Item	Record	Notes
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Kaitlyn Nguyen from ViiV Healthcare regarding Cabenuva. She discussed the public health challenges of HIV and the national goal of reducing new HIV infections by as much as 90% by 2030. Dr. Nguyen noted the challenges of oral antiretroviral regimens. The advantages of injectable therapy were presented, and the importance of open access to Cabenuva. Comment was provided by Mr. John Phoenix regarding Cabenuva and the effective strategy of injectable treatment for patients that struggle with adherence and pill fatigue. Mr. Phoenix requests that Cabenuva be available without any prior authorization restrictions. He notes the importance of quick access to Cabenuva. Written comment was received regarding Cabenuva.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed the drug Cabenuva, including the mechanism of action, indication, administration, and clinical trial demonstrating efficacy. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the Cabenuva. Dr. Eletreby agreed with the proposed criteria and reported low but increasing utilization for Cabenuva. Dr. Bitton agreed with the proposed criteria and noted low utilization for Cabenuva. Mr. Beranek agreed with the proposed criteria and discussed utilization of the different strengths for Cabenuva.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>Board Member Le and Chairwoman Wheeler asked about the operation process to meet the requirement of provider attestation that the patient would benefit from long-acting therapy. Dr. LeCheminant explained attestation would be submitted on the request for prior authorization. For requests with no attestation provided, outreach attempts would be made to obtain attestation from the provider.

Board Member Le recommends removing the provider attestation requirement from the criteria. Chairwoman Wheeler and Board Member Adeolokun voice agreement as the requirement places an unnecessary burden on providers.

Board Member Canty asks if criteria for other medications include provider attestation. Chairwoman Wheeler does not recall other criteria with an attestation requirement. Dr. LeCheminant notes it is becoming less common to add attestation criterion.</td><td></td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Le moved to approve the proposed criteria with the removal that the provider attests the patient would benefit from long-acting injectable therapy over standard oral regimens.

Board Member Tran seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Brian Le, DO</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Michael Owens, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Rebecca Sparks, PA-C ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
e. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Targeted Immunomodulators.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. David Yurick from Bristol Myers Squibb regarding Orencia. He discussed a new indication for Orencia of prophylaxis of acute graft-versus-host disease. Dr. Yurick requested Orencia remain a first-line therapy in the drug class. No written comment was received.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed a new product to the targeted immunomodulator class, Zeposia, the mechanism of action, indication, administration, and clinical trial demonstrating efficacy. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Eletreby agreed with the proposed criteria and reported most utilization is for Humira. Dr. Bitton agreed with the proposed criteria and reported high utilization for Humira. Mr. Beranek disagreed with the proposed criteria and recommended the addition of a documented Mayo Score $\geq$ 6. He reported high utilization for Humira.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members.	

Agenda Item	Record	Notes
	No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member England moved to approve the criteria as presented. 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. ☐ Dave England, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Brian Le, DO: Yes ☒ No ☐ Abst. ☐ Michael Owens, MD: Yes ☒ No ☐ Abst. ☐ Rebecca Sparks, PA-C: Yes ☒ No ☐ Abst. ☐ Jim Tran, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
f. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Respiratory Monoclonal Antibody Agents		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Ben Droese from Amgen Medical Affairs regarding Tezspire. He discussed clinical indication and Tezspire's novel approach to treat severe asthma. Dr. Droese commented on clinical trials demonstrating efficacy. He requested Tezspire be added as a preferred option	

Agenda Item	Record	Notes
	Comment was provided by Dr. Michele Puyear, with Genentech, regarding Xolair. She requested criteria be updated to reflect the new indication of nasal polyps. She noted dosing and clinical efficacy in nasal polyps. Written comment was received regarding Xolair.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed the new indication of Dupixent for treatment of moderate to severe asthma in patients ≥ 6 years of age. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Eletreby agreed with the proposed criteria and highlighted the utilization of Dupixent and Xolair. Dr. Bitton agreed with the proposed criteria and highlighted the high utilization of Dupixent. Xolair utilization via medical is higher than all other agents. Mr. Beranek agreed with the proposed criteria and highlighted the utilization of Dupixent and Xolair.	
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 Le moved to approve the criteria as presented. Board Member Owens seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair — Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
	Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Rebecca Sparks, PA-C ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
g. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Neuropathic Pain and Fibromyalgia Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was provided. No written comment was received	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed Qutenza's use for diabetic peripheral neuropathy. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Eletreby agreed with the proposed criteria and highlighted the utilization of Dupixent and Xolair. Dr. Bitton agreed with the proposed criteria and recommended additional step therapy for the amendment to the criteria. Dr. LeCheminant agreed with the addition of step therapy to the criteria.	

Agenda Item	Record	Notes
	Mr. Beranek agreed with the proposed criteria, Dr. Bitton's updates, and provided that no utilization for this product was noted.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. Board Member Canty discussed removing tricyclic antidepressants from the criteria as they are not often used or recommended for neuropathic pain. Dr. LeCheminant clarified the motion that PA criteria would be updated to include the addition of a trial and failure of preferred lidocaine patch and a trial of either gabapentin, pregabalin, or duloxetine.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member England moved to approve the criteria as presented with removing the requirement that the medication must be prescribed by a Neurologist or Pain Specialist. Board Member Le 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. ☐ Dave England, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Brian Le, DO — Yes ☒ No ☐ Abst. ☐ Michael Owens, MD — Yes ☒ No ☐ Abst. ☐ Rebecca Sparks, PA-C — Yes ☒ No ☐ Abst. ☐ Jim Tran, Pharm.D. — Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
h. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Duchenne Muscular Dystrophy.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Public comment was provided by Dr. Tracy Copeland from Sarepta regarding Amondys 45. She provided clinical indication, the rationale for accelerated approval, and clinical trials demonstrating efficacy. Public comment was provided by Dr. Kathryn Lanza, a Medical Science Liaison from NS Pharma, regarding Viltepso. She provided clinical indication, the rationale for accelerated approval, and noted that most patients are treated for symptom management. Dr. Lanza discussed the mechanism of action, safety, efficacy, and tolerability. She noted that complete product information could be found at Viltepso.com. No written comment was received.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant provided clinical information for Amondys 45. She noted clinical trial information, accelerated approval, dosing, and administration. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Eletreby agreed with the proposed criteria and noted no utilization.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>Dr. Bitton agreed with the proposed criteria and highlighted a small amount of Exondys use.

Mr. Beranek disagreed with the proposed criteria and recommended criteria be added regarding inadequate response despite adherent use of an oral corticosteroid and a requirement for member assessment. He noted no utilization in the drug class.</td><td></td></tr>
<tr><td>iii. Discussion by Board and review of utilization data.</td><td>Chairwoman Wheeler asked for comments from the Board Members.

No comments were made.</td><td></td></tr>
<tr><td>i. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Tran moved to approve the criteria as presented.

Board Member Adeolokun seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Brian Le, DO</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Michael Owens, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Rebecca Sparks, PA-C</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jim Tran, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
<tr><td>5. DUR Board Requested Reports</td><td></td><td></td></tr>
<tr><td>a. <u>For Possible Action</u>: Opioid utilization – top prescriber and members.</td><td></td><td></td></tr>
</table>

Agenda Item	Record	Notes
i. Presentation of opioid criteria		
ii. Discussion by the Board and review of utilization data.	Dr. Lecheminant presented the opioid utilization report. She summarized the opioid 12-month trend. Dr. Lecheminant discussed the patient diagnoses of the top utilizers. She noted a change in the top three prescribers and that the top prescriber is the same hospitalist that was the top prescriber from the last report in October. Dr. Eletreby presented opioid utilization trends and identified a steady morphine equivalent dosing (MED) level over time. She discussed the top providers and top utilizers. Dr. Bitton presented opioid utilization trends. He noted a slight downward trend in opioid scripts and discussed the top prescribers, top members, and how the two lists correlate. Mr. Beranek presented opioid utilization trends highlighting a decrease in utilization. He noted little change in the top ten prescribers and discussed member diagnosis for the top ten utilizers.	
iii. Requests for further evaluation of proposed clinical criteria to be presented at a later date.	Board Member Le asked if a cancer diagnosis could be excluded from the report for evaluation. Dr. LeCheminant noted that this might not be possible based on the diagnosis information provided for claims. She stated that she would attempt to review for top members. Dr. LeCheminant inquired if palliative care should also be excluded. Chairwoman Wheeler confirmed from future opioid reporting.	
6. Standard DUR Reports		
a. Review of Prescribing/ Program Trends.		

Agenda Item	Record	Notes
i. Top 10 Therapeutic Classes for Q3 2021 (by Payment and by Claims).	Dr. LeCheminant presented the top classes with similar results over the quarter, with hemostatic agents on the top by spend amount and anticonvulsants in the top by claim count. Dr. Eletreby presented the top classes and highlighted viral vaccines as the top class by claim count. Dr. Bitton presented the top classes and identified viral vaccines as the top class by claim count. Mr. Beranek presented the top drug classes and identified viral vaccines as the top class by claim count.	
b. Concurrent Drug Utilization Review (CDUR).		
i. Review of Q3 2021. ii. Review of Top Encounters by Problem Type.	Dr. LeCheminant highlighted the prospective DUR reports and the interventions. Dr. Eletreby discussed the prospective DUR and the interventions. Dr. Bitton pointed out the prospective DUR report and the interventions. Mr. Beranek pointed out the prospective DUR report and the interventions.	
c. Retrospective Drug Utilization Review (RetroDUR).		
i. Status of previous quarter. ii. Status of current quarter. iii. Review and discussion of responses.	Dr. LeCheminant discussed the retrospective DUR initiatives during the last quarter with members concurrently using an opioid, antipsychotic, and benzodiazepine Dr. Eletreby highlighted the retrospective DUR programs, including asthma and diabetic monitoring.	

Agenda Item	Record	Notes
	Dr. Bitton discussed retrospective DUR initiatives and results, highlighting the gap in care initiatives. Mr. Beranek discussed the retrospective DUR program highlighting outreach to providers regarding dangerous three drug combinations, respiratory overuse, MME benchmark, diabetic underuse, and antiepileptic adherence. He noted overall response rates.	
7. Centers for Medicare and Medicaid Services (CMS) Annual Drug Utilization Review Surveys		
a. Fee-for-Service Annual DUR Survey presented by OptumRx.	Dr. LeCheminant discussed member demographics, RetroDUR initiatives, generic and brand claims, and the top therapeutic classes.	
b. Anthem Blue Cross Blue Shield Healthcare Solutions Annual DUR Survey presentation.	Dr. Eletreby summarized RetroDUR initiatives and controlled substance utilization management.	
c. Health Plan of Nevada Annual DUR Survey presentation.	Dr. Bitton discussed the CDUR expansion program and RetroDUR highlights.	
d. Silver Summit Health Plan Annual DUR Survey presentation.	Mr. Beranek noted the top 10 prior authorizations. He provided an overview of RetroDUR outreach and generic drug utilization.	
8. Closing Discussion		
a. Public Comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Kaitlin Nguyen from ViiV Healthcare regarding the proposed Cabenuva criteria. She highlighted that Cabenuva does not require a minimum duration of suppression and could be a treatment switch option regardless of how long they were treatment suppressed. She requested the removal of a minimum duration requirement from the criteria.	

Agenda Item	Record	Notes
b. **For Possible Action**: Date and location of the next meeting.	Chairwoman Wheeler stated the next meeting is scheduled for April 28, 2022.	
c. Adjournment.	The meeting adjourned at 3:23 p.m.	

Attachment A – Members of the Public in Attendance

Allen, Lisa, VRTX
Ashton, Elisa, JNJ
Berry, Kenneth, Alkermes
Booth, Robert, Abbvie
Bouluanne-Larsen, Carla
Canavan, Eric, Sarepta
Oliver, Carmen, Biohaven
Case, Lea, Belzcase
Colabianchi, Jeana, Sunovion
Cooper, Christa, Lily
Cooper,Emily, NS Pharma
Copeland, Tracey, Sarepta
Cowan, Sarah
Crecco, Jason
Donahue, Cheryl
Droese, Ben, Amgen
Duke, Michelle
Dzwilewski, Georgette, Indivior
Germain, Joe, Biogen
Goddard, John, GSK
Gonzales, Becky, ViiV
Hawkins, Tina, Magellan
Heinen, Gina, Novo Nordisk
Henry, Lawrence, Fidelis Rx
Hertzberg, Susan, Gene
Jensen, Kathryne, Artia
Johnson, Tory
Kerr, Camille, Regeneron
Lanza, Kathryn, NS Pharma
Leroue, Chelsea, Biohaven
Lovan, Charlie, AbbVie
Maynard, Kelly
McKinnon, Dr. Jonathan
McSherry, Dana, MWE
Morgan, Suzanne, NS Pharma
Nelson, Ann, Vertex
Nguyen, Kaitlin, ViiV
Nguyen, Bao, JNJ
Odebiyi, Olawemimo, Teva
Ou, Karen, Gilead
Pearce, Robert, Teva
Perkins, Carol, Magellan
Phoenix, John, Huntridge
Puyear, Michele, Genentech
Quon, Warren
Ritter, Jean, Zealand
Robinson, Lovell, AbbVie
Rochelle, Yang, Teva

Roy, Melissa, Otsuka
Santarone, Christopher, BMS
Shear, Jennifer, Teva
Sommers, Melissa, Novartis
Stout, Melissa, Chiesi
Sullivan, Mike, Amagen
Tackes, Pierron
Ward, Samantha, Amagen
White, Rianna, Fidelis Rx
Yamashita, Kelvin
Yang, Rochelle, Teva
Yurick, David, BMS
Zarob, Michael, Alkermes

Attendees with no last name available:
Craig

Attachment B – Submitted Written Comment

- 6086 CABENUVA Product Summary
- Cabenuva Prescribing Information
- Hetlioz_NV DURB 1-27 Public Comment
- Xolair_Public Comment

Clinical Presentations

Optum

Prior Authorization Guideline

Guideline Name: Austedo

1 . Indications

Drug Name: Austedo (deutetrabenazine)
Chorea associated with Huntington's disease Indicated for the treatment of chorea associated with Huntington's disease. **Tardive Dyskinesia** Indicated for tardive dyskinesia in adults.

2 . Criteria

Product Name: **Austedo**	
Diagnosis	Chorea associated with Huntington's disease
Approval Length	12 months
Therapy Stage	Initial Authorization

Approval Criteria

1 - Diagnosis of chorea associated with Huntington's disease

AND

2 - Prescribed by or in consultation with a neurologist

AND

3 - The member is 18 years of age or older

Product Name: **Austedo**	
Diagnosis	Chorea associated with Huntington's disease
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Documentation of positive clinical response to therapy

Product Name: **Austedo**	
Diagnosis	Tardive Dyskinesia
Approval Length	3 months
Therapy Stage	Initial Authorization

Approval Criteria

1 - Diagnosis of moderate to severe tardive dyskinesia (TD)

AND

2 - The recipient is 18 years of age or older.

AND

3 - Prescribed by or in consultation with a neurologist or psychiatrist

AND

4 - One of the following:

4.1 Patient has persistent symptoms of tardive dyskinesia despite a trial of dose reduction, tapering, or discontinuation of the offending medication

OR

4.2 Patient is not a candidate for a trial of dose reduction, tapering, or discontinuation of the offending medication

Product Name: **Austedo**	
Diagnosis	Tardive Dyskinesia
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Documentation of positive clinical response to therapy

Optum

Prior Authorization Guideline

Guideline Name: Ingrezza

1 . Indications

Drug Name: Ingrezza (valenazine)
Tardive Dyskinesia (TD) Indicated for the treatment of adults with tardive dyskinesia.

2 . Criteria

Product Name: **Ingrezza**	
Diagnosis	Tardive Dyskinesia
Approval Length	3 Month
Therapy Stage	Initial Authorization

Approval Criteria

1 - Diagnosis of moderate to severe tardive dyskinesia (TD)

AND

2 - The recipient must be 18 years of age or older

AND

3 - Prescribed by or in consultation with a neurologist or psychiatrist

AND

4 - One of the following:

4.1 The recipient must have persistent symptoms of TD despite a trial of dose reduction, tapering or discontinuation of the offending medication

OR

4.2 The recipient must not be a candidate for a trial of dose reduction, tapering or discontinuation of the offending medication

Product Name: **Ingrezza**	
Diagnosis	Tardive Dyskinesia
Approval Length	12 Month
Therapy Stage	Reauthorization

Approval Criteria

1 - Documentation of positive clinical response to therapy

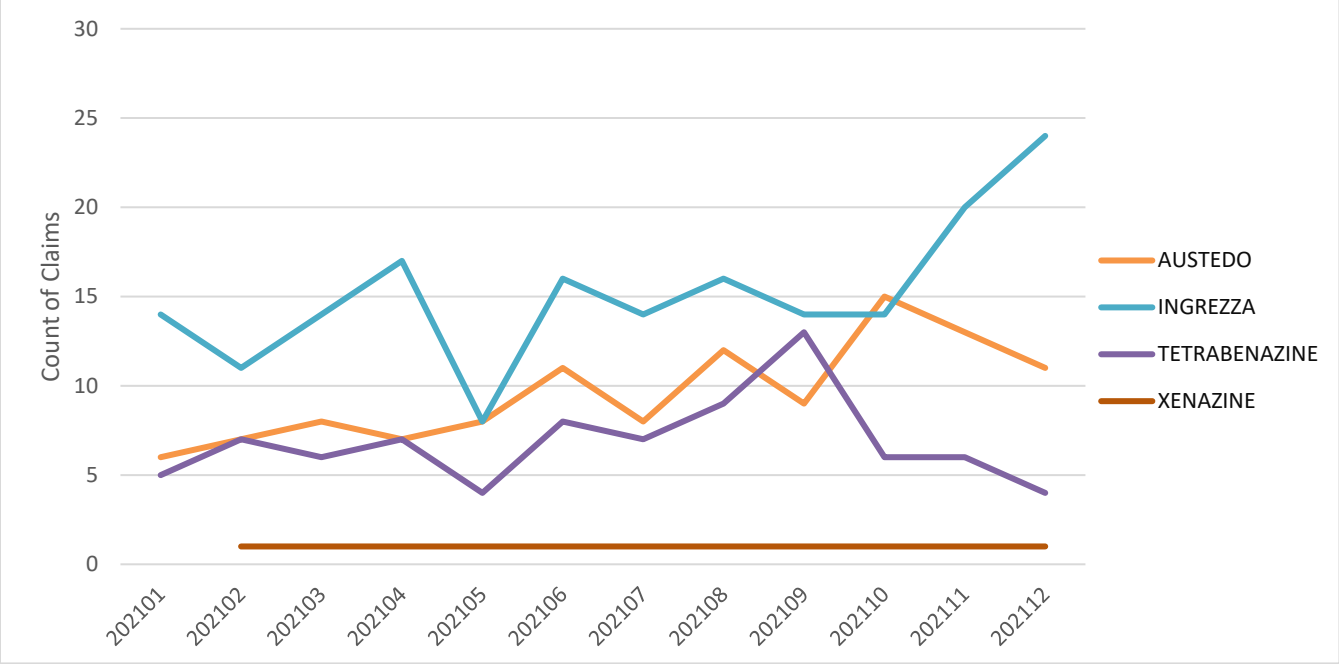
Nevada Medicaid

Utilization

Fee for Service

January 1, 2021 – December 31, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
AUSTEDO	23	115	3,222	7,922
INGREZZA	39	182	5,330	5,330
TETRABENAZINE	12	82	2,162	4,672
XENAZINE	1	11	330	1,320



Therapeutic Class Overview
Movement Disorder Agents

INTRODUCTION

- Huntington disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and neuropsychiatric disturbances (*Coppen and Roos 2017*).
  - Motor dysfunction in HD may include involuntary movements (eg, chorea, dystonia, and tics) and voluntary movements (eg, bradykinesia, apraxia, and motor impersistence) (*Austedo dossier 2017, Coppen and Roos 2017*).
    - Choreic movements are rapid and unpredictable contractions of the facial muscles, trunk, and extremities which vary in frequency, intensity, and amplitude (*Austedo dossier 2017, Suchowersky 2018a*).
    - Dystonia is characterized by sustained or intermittent muscle contractions which lead to abnormal posture of the trunk and extremities. It is more commonly observed in advanced disease stages (*Coppen and Roos 2017*).
    - Motor function slowly deteriorates as HD progresses, and chorea may eventually be replaced by bradykinesia and parkinsonism in advanced stages of the disease (*Suchowersky 2018a, Suchowersky 2018b*).
- HD affects an estimated 1 in 7300 individuals (approximately 43,000 people) in the United States. It is a rare and fatal autosomal dominant genetic disorder associated with onset in early adulthood and death within 20 years of symptom onset (*Austedo dossier 2017, Austedo Food and Drug Administration [FDA] Summary Review 2017*).
- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents (DRBAs), predominantly antipsychotics/neuroleptics (first generation antipsychotics [FGAs], also known as typical antipsychotics, as well as second-generation antipsychotics [SGAs], which are also known as atypical antipsychotics) and metoclopramide (*Rana et al 2013*).
  - While the pathophysiology of TD is not well-understood, the most prominent theory suggests chronic exposure to neuroleptics results in dopamine-2 (D2) receptor up-regulation with postsynaptic dopamine receptor supersensitivity (*Waln and Jankovic 2013*).
  - Prospective studies of patients treated with FGAs suggest that the annual incidence of TD is between 3 to 8%. With SGAs, the mean annual incidence is estimated at 2.1 to 4.2%. Although TD prevalence has been less studied with metoclopramide, the published data indicate a prevalence ranging from 1 to 10% (*Waln and Jankovic 2013*).
- TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area (*Muller et al 2015*). Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Rana et al 2013*).
- According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for ≥ 3 months (or 1 month in patients ≥ 60 years of age) or within 4 weeks of withdrawal from an oral medication (or within 8 weeks of withdrawal from a depot medication). The disorder should persist for ≥ 1 month after discontinuation of an offending drug to qualify as TD (*Waln and Jankovic 2013*).
- The first step in the treatment of TD is to discontinue the offending agent via slow taper. Sudden withdrawal of the offending drug should be avoided, as symptoms of TD could worsen. In patients with psychiatric conditions which require continued use of a neuroleptic, switching from an FGA to an SGA should be considered. Quetiapine and clozapine are the preferred SGAs due to their low receptor occupancy and fast dissociation from D2 receptors (*Vijayakumar and Jankovic 2016*).
- Ingrezza (valbenazine), the first vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of TD, was FDA-approved on April 7, 2018. Prior to valbenazine's approval, Xenazine (tetrabenazine) and Austedo (deutetrabenazine) were FDA-approved for the treatment of Huntington's chorea in August 2008 and April 2017, respectively. Subsequently, deutetrabenazine received FDA approval for the treatment of TD in August 2017.
  - Deutetrabenazine is a chemically modified form of tetrabenazine with deuterium substituted for hydrogen at specific positions. Compared to tetrabenazine, deutetrabenazine reaches comparable systemic exposure with smaller doses, longer treatment intervals, and lower peak concentrations (*Austedo dossier 2017*, *Coppen and Roos 2017*).
    - While deutetrabenazine has been designated a new molecular entity and an orphan drug, it was approved through the 505(b)(2) pathway with tetrabenazine as the Reference Listed Drug (RLD) (*Austedo FDA Summary Review 2017*).

- Differences between valbenazine and deutetrabenazine include once-daily dosing (vs twice-daily dosing) and the absence of a boxed warning for depression and suicidality in patients with HD. Of note, valbenazine has not been studied in patients with HD.

- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Austedo (deutetrabenazine)	-
Ingrezza (valbenazine)	-
Xenazine (tetrabenazine)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Austedo (deutetrabenazine)	Ingrezza (valbenazine)	Xenazine (tetrabenazine)
Chorea associated with HD	✔		✔
Treatment of adults with TD	✔	✔	

(*Prescribing information: Austedo 2017, Ingrezza 2018, Xenazine 2017)*

- 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

Huntington Disease (HD)

- The approval of deutetrabenazine was supported by the First-Time Use of Austedo in HD (First-HD) study conducted by the Huntington Study Group (HSG). The Phase 3, double-blind (DB), multicenter (MC), randomized controlled trial (RCT) compared deutetrabenazine with placebo for 12 weeks, followed by a 1-week washout in 90 adults with HD (*HSG 2016*).
  - The study included patients with a Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score ≥ 8 at baseline and a UHDRS total functional capacity score ≥ 5 at screening (TMC score ranges from 0 to 28, with higher scores indicating more severe chorea) (*Coppen and Roos 2017, Geschwind and Paras 2016*).
  - The primary endpoint was the change from baseline in UHDRS-TMC score.
    - The placebo-adjusted mean change from baseline in TMC with deutetrabenazine was -2.5 points (95% confidence interval [CI], -3.7 to -1.3; $p < 0.001$).
    - In the deutetrabenazine group, the mean TMC scores improved by -4.4 points from 12.1 (95% CI, 11.2 to 12.9) to 7.7 (95% CI, 6.5 to 8.9) over 12 weeks. In the placebo group, mean TMC scores improved by -1.9 points from 13.2 (95% CI, 12.2 to 14.3) to 11.3 (95% CI, 10.0 to 12.5).
  - Four secondary endpoints were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 36-Item Short Form (SF-36) physical functioning subscale score, and Berg Balance Test (BBT). For the PGIC and CGIC, treatment success was defined as an answer of "much" or "very much" improved overall HD symptoms at week 12.
    - The proportion of patients who reported treatment success on the PGIC was 31.1% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The proportion of clinicians who reported treatment success on the CGIC was 28.9% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The placebo-adjusted improvement in the SF-36 physical functioning subscale was 4.34 points with deutetrabenazine ($p = 0.03$).
    - BBT improvement observed with deutetrabenazine did not achieve statistical significance over placebo ($p = 0.14$).
  - In the First-HD study, the incidence of overall, psychiatric, and nervous system adverse events (AEs) was similar between the deutetrabenazine and placebo groups.

  - While generally mild to moderate, AEs resulted in dose reductions for 3 patients (6.7%) in each group. Serious AEs resulted in drug suspension for 1 patient (2.2%) in each group.
  - Somnolence and diarrhea were reported more frequently with deutetrabenazine than with placebo.
- The Phase 3, open-label (OL), MC, long-term Alternatives for Reducing Chorea in HD (ARC-HD) study evaluated the safety and efficacy of deutetrabenazine in 112 patients in 2 cohorts (*Austedo dossier 2017, Frank et al 2017*).
  - The rollover cohort included 75 patients from the First-HD study who underwent washout of deutetrabenazine or placebo. The switch cohort included 37 patients previously on tetrabenazine who were switched overnight to deutetrabenazine at approximately half their previous tetrabenazine dose.
  - Patients in the switch cohort demonstrated improved TMC from baseline with deutetrabenazine 8 weeks following conversion (-2.0 points, $p < 0.001$). Improvements in TMC from baseline were also observed in the rollover cohort at week 2 (-1.9; $p < 0.0001$; n = 58) and maintained through week 28 (-4.4; $p = 0.0055$; n = 14). Common AEs included somnolence, falls, depression, and insomnia.
- A DB, RCT was conducted in 84 ambulatory patients with HD who received tetrabenazine at a maximum dose of 100 mg daily (n = 54) or placebo (n = 30) for 12 weeks. Tetrabenazine treatment resulted in a statistically significant reduction in chorea severity, measured as a change in the chorea score of the UHDRS, compared with placebo (5 unit reduction [tetrabenazine group] vs 1.5 unit reduction [placebo]; adjusted mean effect size -3.5; 95% CI, -5.2 to -1.9; $p < 0.0001$). This change represented a clinically meaningful 24% reduction in chorea from baseline severity. There were 5 study withdrawals and 5 serious AEs in 4 patients (suicide, complicated fall, restlessness/suicidal ideation, and breast cancer) in the tetrabenazine group, compared to 1 withdrawal and no serious AEs in the placebo group (*HSG 2006*).

Tardive Dyskinesia (TD)

- The safety and efficacy of deutetrabenazine was established in the ARM-TD and AIM-TD trials, which were 12-week DB, placebo-controlled (PC), MC, RCTs. Both studies evaluated the change from baseline in items 1 to 7 of the Abnormal Involuntary Movement Scale (AIMS) score as the primary efficacy endpoint. The AIMS total score ranges from 0 to 28, and a decreased score indicates improvement (*Anderson et al 2017, Fernandez et al 2017*).
  - The Phase 2/3 ARM-TD study randomized 117 adults with moderate to severe TD to receive deutetrabenazine titrated to an optimal dose or placebo. The mean dose of deutetrabenazine at the end of titration was 38.8 mg/day. Significant reductions in AIMS scores were observed in patients who received deutetrabenazine compared to placebo (*Fernandez et al 2017*).
    - The least squares mean AIMS score improved by -3.0 points in the deutetrabenazine group vs -1.6 points in the placebo group (treatment difference -1.4; 95% CI, -2.6 to -0.2; $p = 0.019$).
    - Secondary endpoints included proportion of patients who experienced treatment success at week 12 on the CGIC and PGIC. Although CGIC and PGIC results were numerically higher for the deutetrabenazine group, the difference was not statistically significant.
    - The rates of AEs were similar between the deutetrabenazine and placebo groups, including depression and suicidal ideation.
  - The Phase 3 AIM-TD study randomized 298 adults with TD to receive 1 of 3 fixed doses of deutetrabenazine (12, 24, or 36 mg/day) or placebo. Significant reductions in AIMS scores were observed in patients who received 24 or 36 mg of deutetrabenazine per day (*Anderson et al 2017*).
    - The least squares mean AIMS score improved by -3.3, -3.2, -2.1, and -1.4 points in the deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo groups, respectively. The treatment difference was -1.9 points (95% CI, -3.09 to -0.79; $p = 0.001$) with deutetrabenazine 36 mg/day, -1.8 points (95% CI, -3.00 to -0.63; $p = 0.003$) with deutetrabenazine 24 mg/day, and -0.7 points (95% CI, -1.84 to 0.42; $p = 0.217$) with deutetrabenazine 12 mg/day.
    - The overall rate of AEs was similar between groups (51%, 44%, 49%, and 47% for deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo, respectively).
    - Rates of depression, depressed mood, and suicidal ideation were low in all treatment arms; no dose-response relationship was detected.
- The FDA approval of valbenazine was based on the results from the KINECT 3 trial, a 6-week, phase 3, DB, PC, MC, RCT with 224 patients with moderate to severe TD. Patients received valbenazine 40 mg once daily, valbenazine 80 mg once daily, or placebo (*Hauser et al 2017, FDA Ingrezza Medical Review*).
  - In this trial, 85.5% received concomitant antipsychotics (16.7% on FGAs and 76.7% on SGAs). The mean baseline AIMS dyskinesia score was 10.0 (range 0 to 20) between the treatment groups.

- The primary endpoint, which was a modified version of the AIMS score, included 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia).
  - At week 6, the AIMS dyskinesia score was reduced by 3.2 in the valbenazine 80 mg group compared to 0.1 in the placebo group ($p < 0.001$). In the valbenazine 40 mg group, the AIMS dyskinesia score decreased by 1.9 compared to 0.1 in the placebo group ($p = 0.002$).
- The percentage of patients who achieved an AIMS response (defined in the trial as a reduction of ≥ 50% from baseline score) was 40.0% in the 80 mg group ($p < 0.001$) and 23.8% in the 40 mg group ($p = 0.02$), compared to 8.7% in the placebo group.
- The key secondary endpoint of mean Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) score, which investigators used to rate the overall change in TD at week 6, did not reach statistical significance for either valbenazine dosage group when compared to placebo ($p = 0.056$ and $p = 0.074$ for valbenazine 80 mg and 40 mg, respectively).
- The mean PGIC score, which characterized the patient's perception of improvement in their TD symptoms, was slightly worse in both valbenazine treatment groups compared to placebo at week 6; however, the differences did not reach nominal statistical significance.
- The most common AEs observed with valbenazine (both dosage groups combined) vs placebo were somnolence (5.3% vs 3.9%), akathisia (3.3% vs 1.3%), and dry mouth (3.3% vs 1.3%). Suicidal ideation was the most common AE in the placebo group (5.3% vs 2.6% in both valbenazine groups combined).

- A meta-analysis was conducted using two 12-week DB, PC, RCTs with deutetrabenazine (12 to 48 mg/day) (n = 413) and four 4 to 6 week DB, RCTs with valbenazine (12.5 to 100 mg/day) (n = 488). With respect to AIMS scores, both deutetrabenazine (standardized mean difference [SMD] -0.40; 95% CI, -0.19 to -0.62; $p < 0.001$; weighted mean difference [WMD] -1.44; 95% CI, -0.67 to -2.19; $p < 0.001$) and valbenazine (SMD -0.58; 95% CI, -0.26 to -0.91; $p < 0.001$; WMD -2.07; 95% CI, -1.08 to -3.05; $p < 0.001$) demonstrated statistically significant improvement over placebo. Results were confirmed regarding responder rates (≥ 50% AIMS total score reduction for deutetrabenazine: risk ratio [RR] 2.13; 95% CI, 1.10 to 4.12; $p = 0.024$; number-needed-to-treat [NNT], 7; 95% CI, 3 to 333; $p = 0.046$; valbenazine: RR 3.05; 95% CI = 1.81 to 5.11; $p < 0.001$; NNT, 4; 95% CI, 3 to 6; $p < 0.001$). Inconsistent improvements were noted in PGIC ($p = 0.15$) and CGIC scores for deutetrabenazine ($p = 0.088$), and for CGIC scores for valbenazine ($p = 0.67$). In a 54-week, OL extension study of deutetrabenazine and a dose-blinded valbenazine study (48 weeks), responder rates increased over time. No increase in cumulative or specific AEs vs placebo was observed (*Solmi et al 2018*).

CLINICAL GUIDELINES

Huntington Disease (HD)

- **American Academy of Neurology (AAN):** Pharmacologic treatment of chorea in HD (*Armstrong and Miyasaki 2012*)
  - Whether chorea requires treatment should be an individualized decision for providers and their patients with HD.
    - While some studies reported that improving chorea decreases disability or increases quality of life, other studies failed to show an association between chorea and functional decline in HD.
    - The impact of chorea on quality of life should be weighed against other issues, including mood disturbance, cognitive decline, AEs, and polypharmacy risks.
  - For HD chorea which requires pharmacological management, tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) are recommended.
    - Tetrabenazine likely provides very important antichoreic benefits, and riluzole 200 mg/day likely provides moderate benefits. The degree of benefit is unknown for amantadine.
    - Patients on tetrabenazine should be monitored for parkinsonism and depression/suicidality while patients on riluzole should be monitored for elevated liver enzymes.
  - Nabilone may be used for modest decreases in HD chorea, but there is insufficient evidence to recommend long-term use, particularly given concerns for abuse potential.
  - While neuroleptic agents (eg, clozapine) may be reasonable options with a historical suggestion of antichoreic benefit, formal recommendations are not provided due to a lack of studies with sufficient sample sizes and validated outcome measures.
  - The guideline has not been updated since the FDA approval of deutetrabenazine.

Tardive dyskinesia (TD)

- As a follow-up to the 2013 AAN evidence-based treatment guidelines for tardive syndromes (TS) (*Bhidayasiri et al 2013*), Bhidayasiri published a treatment algorithm based on a systematic review of the literature for TS in 2018. Published studies were evaluated for effectiveness of pharmacologic and surgical treatments for TS from 2012 to 2017, using the same rating system ranging from A (highest level of evidence for effectiveness) to U (insufficient evidence) (*Bhidayasiri et al 2018*).
  - While the 2013 guidelines did not make any Level A recommendations, the 2018 update recommends the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A treatment options. Tetrabenazine may be used only if new VMAT2 inhibitors are unavailable.
  - If TS remains troublesome, treatment with a Level B (recommendation should be done based on benefit/risk profile) recommendation, such as gingko biloba extract or clonazepam, should be utilized.
  - If TS continues to be troublesome, short-term amantadine, tetrabenazine, deep brain stimulation, or globus pallidus interna may be tried (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice).
  - There continues to be insufficient evidence to support or refute TS treatment by withdrawing causative agents or switching from typical to atypical DRBAs (Level U).

SAFETY SUMMARY

- **Contraindications**
  - Deutetrabenazine and tetrabenazine are contraindicated in the following populations:
    - Patients with HD who are actively suicidal, or have untreated or inadequately treated depression
    - Patients with hepatic impairment
    - Patients concurrently on monoamine oxidase inhibitors (MAOIs) or who have discontinued MAOI therapy within 14 days
    - Patients concurrently on another VMAT2 inhibitor
  - Valbenazine has no contraindications.
- **Warnings/precautions**
  - **Boxed warning** for deutetrabenazine and tetrabenazine**:** Depression and suicidality in patients with HD
    - Patients with HD have a greater risk of depression and suicidality. Treatment with deutetrabenazine may further increase this risk in patients with HD. Patients on deutetrabenazine should be closely monitored for worsening depression, suicidal thoughts, or unusual changes in behavior.
  - Additional key warnings and precautions for deutetrabenazine and tetrabenazine include:
    - Clinical worsening (eg, decline in mood, cognition, rigidity, and functional capacity) and AEs (eg, sedation, depression, parkinsonism, akathisia, restlessness, cognitive decline) in patients with HD
    - Neuroleptic malignant syndrome (NMS) in patients with HD and TD
      - NMS is a potentially fatal syndrome associated with hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. While NMS has not been observed with deutetrabenazine, it has been observed with its RLD, tetrabenazine. Deutetrabenazine should be discontinued immediately if NMS occurs.
    - Akathisia, agitation, and restlessness in patients with HD and TD
      - In the First-HD study, akathisia, agitation, or restlessness was reported by 4% of patients treated with deutetrabenazine and 2% of patients on placebo. In patients with TD, 2% of patients treated with deutetrabenazine and 1% of patients on placebo experienced these events.
    - Parkinsonism in patients with HD
      - Patients with HD often develop rigidity as part of their underlying disease progression. Drug-induced parkinsonism may cause more functional impairment than untreated chorea. Patients who develop parkinsonism during treatment with deutetrabenazine should reduce their dosage.
    - Sedation and somnolence (also a warning for valbenazine)
      - Sedation is a common dose-limiting AE with deutetrabenazine. In the First-HD study, 11% of patients treated with deutetrabenazine reported somnolence compared with 4% of patients on placebo.
    - QTc prolongation (also a warning for valbenazine)
- **Adverse effects**

- The most common AEs (incidence > 8% and greater than placebo) with deutetrabenazine in the First-HD study included somnolence, diarrhea, dry mouth, and fatigue. In the TD studies, the most common AEs (incidence > 3% and greater than placebo) with deutetrabenazine included nasopharyngitis and insomnia.
- The most common AEs (incidence > 10% and at least 5% greater than placebo) with tetrabenazine included sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, and nausea.
- The most common AEs (incidence ≥ 2%) with valbenazine included somnolence, anticholinergic AEs (dry mouth, constipation, blurred vision, urinary retention), balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

- **Drug Interactions**
  - Deutetrabenazine and tetrabenazine
    - These agents are contraindicated in patients taking MAOIs, reserpine, or other VMAT2 inhibitors.
    - Strong cytochrome P450 (CYP) 2D6 inhibitors increase the systemic exposure to the metabolites of these agents.
    - Concurrent use with neuroleptic drugs (ie, dopamine antagonists, antipsychotics) may increase risk for parkinsonism, NMS, and akathisia.
    - Concomitant use with other drugs that are known to cause QT prolongation should be avoided.
  - Valbenazine
    - Concomitant use of an MAOI is not recommended.
    - Concomitant use with strong CYP3A4 inducers is also not recommended, as this could lead to reduced levels of valbenazine.
    - Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Austedo (deutetrabenazine)	Tablets	Oral	Twice daily	Initial daily dose: 6 mg (HD) or 12 mg (TD); maximum daily dose = 48 mg; dose should be titrated at weekly intervals; administer with food
Ingrezza (valbenazine)	Capsules	Oral	Daily	A lower dose should be administered in patients with moderate to severe hepatic failure
Xenazine (tetrabenazine)	Tablets	Oral	1 to 3 times daily (depending on dose)	Dose should be titrated slowly at weekly intervals and individualized; titration should be stopped or slowed down if patient experiences AEs; patients who require > 50 mg/day should first be tested to determine if they are poor or extensive metabolizers

See the current prescribing information for full details

CONCLUSION

- Deutetrabenazine represents an additional oral therapeutic option for patients with TD or chorea associated with HD.
  - For HD chorea, deutetrabenazine is comparable in safety and efficacy to its RLD, tetrabenazine. The use of both products in HD is limited by dose-related AEs (eg, somnolence, parkinsonism) and a boxed warning for depression and suicidality in a population that is already at a significantly increased risk.

- The first step in the treatment of TD is to discontinue the offending agent by slow taper. The patient can switch to quetiapine and clozapine (SGA of choice) if needed.
- The First-HD study, which compared deutetrabenazine with placebo for 12 weeks demonstrated a statistically significant improvement in the TMC score in the deutetrabenazine group compared to placebo. Secondary endpoints such as PGIC and CGIC also showed improvement.
- The KINECT 3 trial demonstrated a significant reduction in AIMS dyskinesia score of -3.2 in the valbenazine 80 mg/day group and -1.9 in the valbenazine 40 mg/day group, however, there were no significant improvements in the CGI-TD score or patient-perceived improvement in function or quality of life.
  - The extension trial continued to demonstrate reductions in AIMS dyskinesia score from baseline to week 48 in both dosage groups.
- The ARM-TD and AIM-TD trials demonstrated significant reductions in AIMS score in patients who received deutetrabenazine compared to placebo.
- For TD, valbenazine is an alternative with the same mechanism of action and a once-daily dosing schedule compared to twice-daily deutetrabenazine.
- The AAN 2012 guideline for the treatment of chorea associated with HD recommends treatment with tetrabenazine, amantadine, or riluzole (Level B; recommendation should be done based on benefit/risk profile). Nabilone may also be used for modest decreases in HD chorea (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U; insufficient evidence). Data are insufficient to make recommendations regarding the use of neuroleptics or donepezil for HD chorea treatment (Level U).
- A treatment algorithm for TS was published in 2018, as a follow-up to the 2013 AAN evidence-based treatment guideline for TS. The most important change in recommendations was related to the addition of the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A (highest level of evidence for effectiveness) treatment options. Tetrabenazine is recommended as an alternative if new VMAT2 inhibitors are unavailable. Gingko biloba and clonazepam continued to be recommended in the Level B category as well as amantadine and tetrabenazine in the Level C category.

REFERENCES

- Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Psychiatry*. 2017:S2215-0366(17)30236-5. doi: 10.1016/S2215-0366(17)30236-5.
- Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2012;79(6):597-603.
- Austedo [AMCP dossier], North Wales, PA: Teva Pharmaceuticals USA, Inc.; May 2017.
- Austedo [package insert], North Wales, PA: Teva Pharmaceuticals; August 2017.
- Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: Treatment of tardive syndromes: Report of the guidelines development subcommittee of the American Academy of Neurology. *Neurology*. 2013;81;463-469.
- Bhidayasiri R, Jitkritsadakul O, Friedman JH, et al. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. *J Neurol Sci*. 2018;389:67-75.
- Coppen EM, Roos RA. Current pharmacological approaches to reduce chorea in Huntington's disease. *Drugs*. 2017;77(1):29-46.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed October 10, 2018.
- Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study. *Neurology*. 2017 May 23;88(21):2003-2010.
- Food and Drug Administration/Center for Drug Evaluation and Research. FDA approved drug products. FDA Austedo summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208082Orig1s000SumR.pdf. March 29, 2017. Accessed October 10, 2018.
- Food and Drug Administration/Center for Drug Evaluation and Research. FDA approved drug products. FDA Ingrezza Medical Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209241Orig1s000MedR.pdf. Accessed October 10, 2018.
- Frank S, Stamler D, Kayson E, et al. Safety of converting from tetrabenazine to deutetrabenazine for the treatment of chorea. *JAMA Neurol*. 2017;74(8):977-982.
- Geschwind MD, Paras N. Deutetrabenazine for treatment of chorea in Huntington disease. *JAMA*. 2016 ;316(1):33-5.
- Hauser RA, Factor SA, Marder SR, et al. KINECT 3: A Phase 3, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017; 174:476–484.
- Huntington Study Group. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. *JAMA*. 2016;316(1):40-50.
- Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology*. 2006;66(3):366-372.
- Ingrezza [package insert], San Diego, CA: Neurocrine Biosciences; August 2018.
- Muller T. Valbenazine granted breakthrough drug status for treating tardive dyskinesia. *Expert Opin Investig Drugs*. 2015;24(6):737-742.

- 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 October 10, 2018.
- Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. *Drug Des Devel Ther.* 2013;7:1329-1340.
- Solmi M, Pigato G, Kane JM, et al. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther.* 2018;12:1215-1238.
- Suchowersky O. Huntington disease: clinical features and diagnosis. UpToDate Web site. www.uptodate.com. Updated July 13, 2018a. Accessed October 10, 2018.
- Suchowersky O. Huntington disease: management. UpToDate Web site. www.uptodate.com. Updated August 24, 2018b. Accessed October 10, 2018.
- Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: Treatment of tardive dyskinesia. *Drugs.* 2016;76:779-787.
- Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov.* 2013;3:1-11.
- Xenazine [package insert], Deerfield, IL: Lundbeck Pharmaceuticals; September 2017.

Publication Date: October 22, 2018

Optum

Prior Authorization Guideline

Guideline Name: Hetlioz, Hetlioz LQ

1 . Indications

Drug Name: Hetlioz (tasimelteon) capsule
Non-24-Hour Sleep-Wake Disorder (Non-24) Indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)
Drug Name: Hetlioz capsule, Hetlioz LQ suspension
Smith-Magenis Syndrome (SMS) Indicated for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in pediatric patients 3 to 15 years of age.

2 . Criteria

Product Name: **Hetlioz capsule**	
Diagnosis	Non-24-Hour Sleep-Wake Disorder (Non-24)
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of non-24-hour sleep-wake disorder (also known as free-running disorder, free-running or non-entrained type circadian rhythm sleep disorder, or hypernychthemeral syndrome) [2,5-6,A] **AND** **2** - Patient is totally blind (has no light perception) [2-8,B] **AND** **3** - Prescribed by or in consultation with a neurologist or a specialist in sleep disorders **AND** **4** - The recipient had an adverse reaction, contraindication, or an inadequate response (after at least four weeks of therapy) to a therapeutic dose of melatonin	

Product Name: **Hetlioz capsule**	
Diagnosis	Non-24-Hour Sleep-Wake Disorder (Non-24)
Approval Length	12 month(s)

Therapy Stage	Reauthorization
Approval Criteria **1** - Documentation of positive clinical response to therapy	

Product Name: **Hetlioz capsule**	
Diagnosis	Smith-Magenis Syndrome (SMS)
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of Smith-Magenis Syndrome (SMS) **AND** **2** - Patient is 16 years of age or older **AND** **3** - Patient is experiencing nighttime sleep disturbances (i.e., difficulty falling asleep, frequent nighttime waking and early waking) **AND** **4** - Prescribed by or in consultation with a neurologist or a specialist in sleep disorders **AND** **5** - The recipient had an adverse reaction, contraindication, or an inadequate response (after at least four weeks of therapy) to a therapeutic dose of melatonin	

Product Name: **Hetlioz LQ suspension**	
Diagnosis	Smith-Magenis Syndrome (SMS)
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of Smith-Magenis Syndrome (SMS) **AND** **2** - Patient is 3 through 15 years of age **AND**	

3 - Patient is experiencing nighttime sleep disturbances (i.e., difficulty falling asleep, frequent nighttime waking and early waking)

AND

4 - Prescribed by a neurologist or a specialist in sleep disorders

AND

5 - The recipient had an adverse reaction, contraindication, or an inadequate response (after at least four weeks of therapy) to a therapeutic dose of melatonin

Product Name: **Hetlioz capsule, Hetlioz LQ suspension**	
Diagnosis	Smith-Magenis Syndrome (SMS)
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Documentation of positive clinical response to therapy (i.e., improvement in nighttime total sleep time, improvement in nighttime sleep quality)

3 . Definitions

Definition	Description
Totally blind	Patients whose blindness is characterized by an inability to perceive any light. Totally blind patients have no light perception. [4]

4 . Endnotes

A. The International Classification of Sleep Disorders (an official publication of the American Academy of Sleep Medicine) defines non-24-hour sleep-wake disorder as a circadian rhythm sleep disorder characterized by complaints of insomnia or excessive sleepiness related to abnormal synchronization between the 24-hour light-dark cycle and the endogenous circadian rhythms of sleep and wake propensity. [2] Patients with non-24 experience a chronic steady pattern comprising 1- to 2-hour daily delays in sleep onset and wake times. As incremental phase delays in sleep occur, the complaint will consist of difficulty initiating sleep at night coupled with oversleeping into the daytime hours or inability to remain awake in the daytime. Therefore, over long periods of time, patients alternate between being symptomatic and asymptomatic, depending on the degree of synchrony between their internal biologic rhythm and the 24-hour world. [2] The condition is very rare in normally sighted people, but quite common in the totally blind who have no access to the entraining effects of the light-dark cycle. [3] Of the estimated 1.3 million legally blind individuals in the United States, approximately 130,000 have no light perception. Epidemiologic studies have found that 57-70% of this totally blind sub-population suffer from non-24. [4] Non-24 is considered a chronic condition and markedly decreases the quality of life for patients. To varying extents, individuals with non-24 are unable to function in scheduled social activities or hold conventional jobs. [2,4]

B. Hetlioz was approved on the basis of two pivotal, randomized, double-masked, placebo-controlled, multicenter, parallel-group studies in totally blind patients with non-24-hour sleep-wake disorder. [1,7] The Safety and Efficacy of Tasimelteon (SET) Trial [1,7] was conducted in 84 totally blind patients with non-24, aged 21-84 years. Subjects received either Hetlioz 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months. The Randomized-withdrawal study of the Efficacy and Safety of Tasimelteon to treat non-24 (RESET) Trial [1,8] was conducted in 20 entrained totally blind patients with non-24, aged 28-70 years. Subjects were treated for approximately 12 weeks with Hetlioz 20 mg one hour prior to bedtime, at the same time every night. Patients in whom the calculated time of peak melatonin level (melatonin acrophase) occurred at approximately the same time of day (in contrast to the expected daily delay) during the run-in phase were randomized to receive placebo or continue treatment with Hetlioz 20 mg for 8 weeks.
C. Given the wide range of available dosing regimens for melatonin, the variability in response time to treatment with tasimelteon and melatonin, and the need for consistent monitoring and evaluation of patients' sleep-related symptoms, tasimelteon must be prescribed by or in consultation with a specialist in sleep disorders.

5 . References

1. Hetlioz prescribing information. Vanda Pharmaceuticals, Inc. Washington D.C. October 2019.
2. The International Classification of Sleep Disorders, Revised: Diagnostic & Coding Manual. Westchester, IL: American Academy of Sleep Medicine; 2001.
3. Sack RL, Auckley D, Auger RR, et al. Circadian rhythm sleep disorders: Part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. Sleep 2007;30(11):1484-1501.
4. Vanda Pharmaceuticals, Inc. About Non-24. Available at: http://www.non-24.com/about-non-24.php. Accessed on July 23, 2015.
5. National Sleep Foundation. Non-24-hour Sleep Wake Disorder Facts and Prevalence. Available at: http://sleepfoundation.org/non-24/facts_prevalence.html. Accessed on July 23, 2015.
6. Circadian Sleep Disorders Network. Non-24-Hour Sleep-Wake Disorder Questions and Answers. Available at: http://www.circadiansleepdisorders.org/docs/N24-QandA.php. Accessed on July 23, 2015.
7. Lockley SW, Dressman MA, Xiao C, et al. Tasimelteon treatment entrains the circadian clock and demonstrates a clinically meaningful benefit in totally blind individuals with non-24-hour circadian rhythms [Poster abstract no. FP26-6]. 95th Annual Meeting of the Endocrine Society; 15-18 Jun 2013; San Francisco, CA.
8. Lockley SW, Dressman MA, Xiao C, Licamele L, Polymeropoulos MH. RESET study demonstrates that tasimelteon maintains entrainment of melatonin and cortisol in totally blind individuals with non-24-hour circadian rhythms [Poster abstract no. SUN-137]. 95th Annual Meeting of the Endocrine Society; 15-18 Jun 2013; San Francisco, CA.

Nevada Medicaid

Utilization

Fee for Service

January 1, 2021 – December 31, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
HETLIOZ	1	1	30	30

INTRODUCTION

- Generalized anxiety disorder (GAD) is a common form of anxiety disorder characterized by excessive and uncontrollable worry that may manifest itself in a number of psychic and somatic symptoms such as irritability, difficulty concentrating, muscle tension, fatigue, and sleep disturbance. To meet Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria, worry and other associated symptoms must be present more days than not for at least 6 months and must adversely affect the patient's life (*Baldwin et al 2018, DSM-V criteria*).
  - According to the National Institutes of Mental Health (NIMH), the 12-month prevalence of GAD is 2.7% in the United States (US) population *(NIMH Web site 2017).*
  - The onset of GAD symptoms may occur before the age of 20. GAD is twice as common in females compared to males, and is the most common anxiety disorder among older patients *(Baldwin et al 2018).*
- Social anxiety disorder (SAD) is characterized by the persistent fear of being observed or evaluated negatively by others in social performance or interaction situations. Patients with SAD often avoid social interactions or endure them with intense anxiety or distress *(Bandelow et al 2012).*
- Panic disorder is a form of anxiety disorder that is characterized by episodic, unexpected panic attacks that occur without a clear trigger. Panic attacks are defined by the rapid onset of intense fear (typically peaking within about 10 minutes) with at least 4 of the physical and psychological symptoms listed in the DSM-V diagnostic criteria (ie, palpitations, sweating, trembling/shaking, sensations of shortness of breath, feelings of choking, chest pain/discomfort, nausea, feeling dizzy or unsteady, chills or heat sensations, paresthesias, derealization, fear of losing control, and fear of dying) *(Locke et al 2015).*
- Effective treatments for GAD include cognitive-behavioral therapy, applied relaxation, and medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) *(Baldwin et al 2018).* Other agents, such as buspirone and hydroxyzine are also recommended as treatment options in clinical guidelines. The medication choice should be made based on several factors, such as efficacy, possible adverse events (AEs), contraindications, and drug interactions *(Bandelow et al 2015).*
  - Benzodiazepines (BZDs) have been widely used in managing GAD because of their rapid onset of action and proven efficacy. They can be helpful as short-term treatment during the period before antidepressants take effect and to help alleviate the restlessness and agitation that can occur with initiation of antidepressant therapy. All of the BZDs are considered to be of equal efficacy for the treatment of GAD *(Gliatto 2000, Locke et al 2015).*
    - BZDs exert their effects through their activity at the gamma-aminobutyric acid type A (GABA) receptors, potentiating the effects of endogenous GABA, the main inhibitory neurotransmitter.
- Insomnia is defined as a complaint of trouble initiating or maintaining sleep, which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep *(Sateia et al 2017).*
  - Insomnia is considered chronic when it has persisted for at least 3 months at a frequency of at least 3 times per week. The prevalence of chronic insomnia in industrialized nations is estimated to be at least 5% to 10%.
  - Insomnia is considered short-term when the disorder meets symptom criteria but has persisted for less than 3 months. Occasional, short-term insomnia is thought to affect 30% to 50% of the population.
- Insomnia often occurs with comorbid disorders, including depression, anxiety, and substance abuse *(Schutte-Rodin et al 2008).*
  - Certain medical or psychiatric disorders may also increase the risk of insomnia; psychiatric and chronic pain disorders have been associated with insomnia in as many as 50 to 75% of patients.
  - Insomnia is also associated with an increased risk of suicide and may result in relapse among prior substance abusers.
- The primary treatment goals are to improve sleep quality and quantity and to improve insomnia-related daytime impairments *(Schutte-Rodin et al 2008).*

- General treatment measures for insomnia include the treatment of comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimizing the sleep environment. Part of the initial approach to treatment should include cognitive behavioral therapy (*Sateia et al 2017, Schutte-Rodin et al 2008)*.
- Prior to the introduction of BZDs, barbiturates and related compounds were commonly used for the management of anxiety and sleep disturbance. The first BZD, chlordiazepoxide, was introduced to the US market in 1963, followed shortly by diazepam. Flurazepam, the first BZD approved as a hypnotic, became available in 1970 and rapidly supplanted the use of barbiturates and other related compounds for the treatment of insomnia. Zolpidem, the first non-BZD hypnotic approved in the US, became available in 1992 and remains the most widely prescribed hypnotic medication *(Sateia et al 2017)*.
- Other than zolpidem, the non-BZD sedative hypnotics used to treat insomnia are doxepin (Silenor), eszopiclone (Lunesta), ramelteon (Rozerem), lemborexant (Dayvigo), suvorexant (Belsomra), tasimelteon (Hetlioz), and zaleplon (Sonata).
  - Ramelteon and tasimelteon are melatonin receptor agonists that possess affinity for the MT1 and MT2 receptors vs. the MT3 receptor. Tasimelteon has a unique indication for treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), a circadian rhythm sleep disorder found predominantly in the blind and characterized by excessive sleepiness during the day and an inability to sleep at night.
  - Doxepin's mechanism of action is not fully understood, but it is thought that antagonism of the H1 receptor is the most likely mechanism by which doxepin exerts it sleep maintenance effect.
  - The remaining agents act at the GABA-receptor.
- All of the agents in this review (with the exception of tasimelteon) have been shown to result in positive effects on sleep latency, total sleep time (TST) and/or wake time after sleep onset (WASO). The BZDs have been shown to be effective in improving sleep latency and TST. Other agents such as zaleplon and ramelteon are effective in reducing sleep latency, whereas medications such as eszopiclone and temazepam are more likely to improve sleep maintenance *(Schutte-Rodin et al 2008)*.
- Although a substantial number of Food and Drug Administration (FDA)- and non FDA-approved anxiolytics and sedative hypnotics are available, the focus of this review will be on BZDs and non-BZDs agents. Other classes of agents such as barbiturates, SNRIs, SSRIs, and tricyclic antidepressants (TCAs) are also utilized in these settings but will not be the focus of this review.
- Several BZDs and some non-BZDs have additional FDA-approved indications such as alcohol withdrawal, seizure disorder, muscle relaxation, and depression. These indications are outside the scope of this review, and therefore will not be addressed in this review.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Benzodiazepines	
Xanax (alprazolam), alprazolam Intensol, alprazolam ODT, Xanax XR (alprazolam extended-release)	✔
chlordiazepoxide	✔ §
Klonopin (clonazepam)	✔
Tranxene-T (clorazepate)	✔
Valium (diazepam), diazepam Intensol	✔
estazolam	✔ §
flurazepam	✔ §
Ativan (lorazepam), lorazepam Intensol	✔
oxazepam	✔ §
Restoril (temazepam)	✔
Halcion (triazolam)	✔
Doral (quazepam)	✔
Non-benzodiazepines	
buspirone	✔ §

Drug	Generic Availability
Silenor (doxepin)	✔
Lunesta (eszopiclone)	✔
Dayvigo (lemborexant)	-
meprobamate	✔
Rozerem (ramelteon)	✔
Belsomra (suvorexant)	-
Hetlioz (tasimelteon)	-
Sonata (zaleplon)	✔
Ambien, Edluar, Intermezzo, Zolpimist (zolpidem) Ambien CR (zolpidem extended-release)	✔ *

* Zolpimist is not available as generic
§ Buspar (buspirone), Dalmane (flurazepam), Librium (chlordiazepoxide), Prosom (estazolam), and Serax (oxazepam) are brands that are no longer marketed

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	BZDs												Non-BZDs									
Indication	**alprazolam**	**chlordiazepoxide**	**clonazepam**	**clorazepate**	**diazepam**	**estazolam**	**flurazepam**	**lorazepam**	**oxazepam**	**temazepam**	**triazolam**	**quazepam**	**buspirone**	**doxepin**	**eszopiclone**	**lemborexant**	**meprobamate**	**ramelteon**	**suvorexant**	**tasimelteon**	**zaleplon**	**zolpidem**
Short term treatment of insomnia characterized by difficulties with sleep initiation/onset																		✔				✔ (Ambien, Edluar, Zolpimist)
Treatment of insomnia, characterized by difficulties with sleep maintenance														✔								
Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance																✔			✔			✔ (Ambien CR)

Treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings						✔ *	✔					✔									
Short-term treatment of insomnia										✔	✔									✔	
Treatment of insomnia														✔							
Treatment of non-24-hour sleep-wake disorder																			✔		
As needed treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep																					✔ (Intermezzo)
Management of anxiety disorder or short-term relief of symptoms of anxiety	✔ (alprazolam Intensol, Xanax)	✔		✔	✔			✔	✔				✔				✔				
Treatment of generalized anxiety disorder	✔ (alprazolam ODT)																				
Treatment of panic disorder, with or without agoraphobia	✔ (alprazolam Intensol, alprazolam ODT, Xanax, Xanax XR)		✔																		
Preoperative apprehension and anxiety		✔																			
Pre-anesthesia to produce sedation, relief of anxiety, and decreased ability to recall events related to surgery								✔													

* Short-term use

(*Prescribing information: alprazolam Intensol 2017, alprazolam ODT 2019, Ambien 2019, Ambien CR 2019, Ativan 2018, Belsomra 2020, buspirone 2017, chlordiazepoxide 2016, Dayvigo 2019, diazepam Intensol 2016, Doral 2019, Edluar 2019, estazolam 2019, flurazepam 2018, Halcion 2019, Hetlioz 2019, Intermezzo 2019, Klonopin 2017, lorazepam*

Intensol 2019, Lunesta 2019, meprobamate 2016, oxazepam 2016, Restoril 2018, Rozerem 2018, Silenor 2019, Sonata 2019, Tranxene-T 2018, Valium 2017, Xanax 2017, Xanax XR 2016, Zolpimist 2019)

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

CLINICAL EFFICACY SUMMARY

- A meta-analysis that examined 105 randomized, double-blind (DB), placebo-controlled (PC) trials was conducted to evaluate safety and efficacy of drug treatments for chronic insomnia in adults. Of these trials, 52 involved BZDs, 48 involved non-BZDs, and 8 involved antidepressants (ADPs). Most of the studies had short-treatment duration (≤ 4 weeks) in the non-elderly population. The primary efficacy measure was sleep onset latency, with WASO as the secondary outcome measure (*Buscemi et al 2007)*.
  - Sleep onset latency was significantly decreased, as compared to placebo, when measured by polysomnography (PSG) for the BZDs (weighted mean difference [WMD]: −10.0 minutes; 95% confidence interval [CI], −16.6 to −3.4), non-BZDs (WMD −12.8 minutes; 95% CI, −16.9 to −8.8) and ADPs (WMD −7.0 minutes; 95% CI, −10.7 to −3.3) as well as when measured by sleep diary (WMD −19.6 minutes; 95% CI, −23.9 to −15.3; WMD −17.0 minutes; 95% CI,−20.0 to −14.0; WMD: −12.2 minutes; 95% CI, −22.3 to −2.2, respectively).
  - WASO, sleep efficiency, TST, and sleep quality were evaluated and subcategorized by PSG and sleep diary. All results were statistically significant and favored BZDs and non-BZDs except for the PSG studies measuring WASO and TST, which were just below the range of significance. The PSG results significantly favored the antidepressants, and the sleep diary results, which were fewer, favored the antidepressants for WASO. Placebo was favored for TST, however, the results did not achieve statistical significance.
  - All treatment groups had a statistically significant incidence of AEs compared to placebo (BZDs risk difference [RD]: 0.15; non-BZDs RD: 0.07; and antidepressants RD: 0.09), although the most commonly reported AEs were considered minor. The most common AEs reported in the BZD group were headache, somnolence, dizziness, nausea, and fatigue while the most common AEs in the non-BZD and ADP groups were headache, dizziness, nausea, and somnolence. Indirect comparisons suggest that BZDs and non-BZDs have similar effects, but that non-BZDs may be safer.
  - The authors noted substantial heterogeneity of data, which was reduced in subgroup analyses by type of drug. Overall, BZDs and non-BZDs were not significantly different with respect to efficacy.
- A meta-analysis of 22 randomized, DB, PC trials evaluated the safety and efficacy of short-term (14 days) BZDs or zolpidem in the treatment of insomnia in adults < 65 years of age (n = 1894). The treatment duration was ≤ 35 days. It was found that BZDs and zolpidem produced significant improvements in the primary outcomes (as measured by PSG and self-reporting) of sleep onset latency, number of awakenings, TST, and sleep quality compared to placebo ($p < 0.001$) and their effect sizes were moderate *(Nowell et al 1997).*
- A 2012 meta-analysis that was published using data on the FDA website examined the efficacy and safety of non-BZDs (eszopiclone, zaleplon, zolpidem) using 13 randomized, DB, parallel-group (PG), PC clinical trials (n = 4378). Non-BZDs showed a small, but significant, improvement (reduction) of 22 minutes (95% CI, −33 to −11) in the primary endpoint of PSG sleep latency. For the other primary outcome of subjective sleep latency, non-BZDs showed a small but statistically significant improvement of 7 minutes, compared to placebo. The analyses of effects size showed significant but small to medium differences in PSG sleep latency (WMD -0.36; 95% CI, −0.57 to −0.16) and subjective sleep latency (WMD -0.33; 95% CI, −0.62 to −0.04). The secondary outcomes of TST, PSG and subjective number of awakenings, subjective sleep onset, and sleep quality did not show significant differences, which may have been due to limited data and reporting in the clinical trials *(Huedo-Medina et al 2012).*
- A 2017 meta-analysis of 31 randomized, PG, PC trials with BZDs, non-BZDs (eszopiclone, zaleplon, zolpidem), melatonin agonists, ADPs and other sedating medications was conducted to compare the efficacy of these medications for treatment of primary insomnia. In this meta-analysis, both BZDs and non-BZDs were significantly more effective than ADPs (including low-dose doxepin) in reducing objective sleep onset latency. Also, BZDs were found to be significantly more effective than non-BZDs in reducing subjective sleep onset latency. Non-BZDs demonstrated higher effect sizes for the primary outcomes of objective sleep onset latency and objective TST. Additionally, the pooled effect sizes for all of the outcome variables were statistically significant, indicating small to medium effects *(Winkler and Doering 2014).*
- A meta-analysis that evaluated 234 studies (n = 37,333) was conducted to determine the most efficacious pharmacological treatments for GAD, panic disorder, and SAD. The authors concluded that various studies with SSRIs

and SNRIs show that they can be efficacious in the management of anxiety. There was also some evidence for the efficacy of certain BZDs, buspirone, imipramine, hydroxyzine and trifluoperazine. BZDs, however, may cause dependency and are therefore not recommended for routine use *(Baldwin and Polkinghorn 2005).*

- A meta-analysis of 8 randomized controlled trials (n = 152) compared the effects of acetazolamide, temazepam, zolpidem, zaleplon, or theophylline on sleep quality in patients with acute exposure to high altitudes. The meta-analysis concluded that zaleplon and zolpidem improved the TST, sleep efficiency index, and stage 4 sleep duration, and these agents decreased WASO compared to placebo or no-treatment. Temazepam showed similar outcomes to placebo for the onset of sleep and sleep quality (*Kong et al 2018*).
- Two 6-month DB, PC, randomized trials (SET and RESET) of tasimelteon in totally blind patients with Non-24 (n = 84) demonstrated that tasimelteon 20 mg given 1 hour before bedtime at the same time every day was well tolerated and entrained the master body clock to a 24-hour clock as measured by urinary 6-sulfatoxymelatonin (aMT6s) and cortisol. During the SET clinical trial, the primary endpoint of sleep entrainment (as measured by aMT6s) was achieved by 20% (8 out of 40) of patients in the tasimelteon group vs. 3% (1 out of 38) of patients in the placebo group (difference of 17%, 95% CI: 3.2 to 31.6, p = 0.0171). A responder analysis demonstrated that 29% of subjects treated with tasimelteon demonstrated clinical response as measured by a ≥ 45-minute improvement in both nighttime and daytime sleep. During the RESET trial, 90% (9 out of 10) of patients in the tasimelteon group vs. 20% (2 out of 10) of patients in the placebo group maintained entrainment (*Lockley et al 2015*).
- A 12-month DB, PG, randomized clinical trial evaluated the safety and efficacy of suvorexant compared to placebo in patients with primary insomnia (n = 781). At Month 1, suvorexant showed greater efficacy than placebo in improving subjective sleep maintenance (TST 22.7 min, 95% CI: 16.4 to 29, p < 0.0001) and subjective time to sleep onset (TSO) (TSO -9.5 min, 95% CI: -14.6 to -4.5, p = 0.0002). These improvements were maintained throughout the 1-year phase (27.5 min in subjective TST, 95% CI: 16.2 to 38.8, p < 0.0001; -9.7 min in subjective TSO, 95% CI: -16.5 to -2.9, p = 0.0055). Over the course of 1 year, the proportion of patients with discontinuation due to AEs or serious AEs was similar among the treatment groups and there was no clinically important difference. The most common AE, somnolence, was reported for 13% of patients who received suvorexant and 3% who received placebo (difference of 10.5%, 95% CI: 6.8 to 14.1) *(Michelson et al 2014).*
- A meta-analysis of 4 randomized controlled trials (n = 3076) revealed improved TSO, subjective TST, and subjective quality of sleep at months 1 and 3 with suvorexant compared with placebo. At 12 months, suvorexant increased subjective TST, quality of sleep, but not TSO. Comparative trials of suvorexant to other agents are lacking (*Kuriyama et al 2017*).
- Two DB, PC, randomized studies evaluated the efficacy of lemborexant in patients with insomnia.
  - SUNRISE 1 randomized 1006 patients to lemborexant (5 mg or 10 mg), zolpidem CR, or placebo for 1 month. Compared with placebo, both doses of lemborexant displayed improved sleep onset from baseline (least squares means [LSM] treatment ratio 0.77; 95% CI, 0.67 to 0.89; p < 0.001 for lemborexant 5 mg, and LSM treatment ratio 0.72; 95% CI, 0.63 to 0.83; p < 0.001 for lemborexant 10 mg) and improved sleep efficiency (LSM treatment difference vs placebo 7.1%; 95% CI, 5.6% to 8.5%; p < 0.001 for lemborexant 5 mg, and LSM difference 8.0%; 95% CI, 6.6% to 9.5%; p < 0.001 for lemborexant 10 mg). Compared with zolpidem, both doses of lemborexant improved wake-after-sleep onset in the second half of the night (LSM treatment difference vs zolpidem -6.7 min; 95% CI, -11.2 to -2.2 min; p = 0.004 for lemborexant 5 mg, and LSM treatment difference -8.0 min; 95% CI, -12.5 to -3.5 min; p < 0.001 for lemborexant 10 mg) (*Rosenberg et al 2019*).
  - In the second study, 971 patients received lemborexant 5 mg, lemborexant 10 mg, or placebo. At 6 months, both doses of lemborexant demonstrated improvement in sleep onset, sleep efficiency, and WASO compared with placebo (p < 0.05 for all comparisons of lemborexant doses vs placebo) (*Dayvigo prescribing information 2019*).
- A meta-analysis with 48 studies was conducted to evaluate the efficacy of pharmacological treatments in GAD. The main drug classes compared were the BZDs (diazepam, lorazepam, alprazolam) and the azapirones (buspirone). The BZDs and azapirones were equally effective for anxiety (effect size for BZDs of 0.32, effect size for azapirones of 0.30), although the compliance rate was higher for the BZDs (24.4% drop-out rate vs. 30.7%, respectively, p < 0.05). The author concluded that BZDs and azapirones are effective for the short-term treatment of anxiety, but no drug class is superior in reducing symptoms *(Mitte et al 2005).*
- A Cochrane review of 24 randomized studies (n = 4233) concluded a possible superiority of BZDs for a response to treatment (risk ratio [RR] 1.65, 95% CI, 1.39 to 1.96) and dropout rate (RR 0.50; 95% CI, 0.39 to 0.64) compared with placebo among adult patients with panic disorder. The quality of the evidence was rated low for both outcomes (*Breilmann et al 2019*).

CLINICAL GUIDELINES

Anxiety

- American Academy of Family Physicians (AAFP) Diagnosis and Management of Generalized Anxiety Disorder and Panic Disorder in Adults *(Locke et al 2015)*
  - First-line pharmacologic therapies
    - SSRIs
    - SNRIs (duloxetine and venlafaxine ER)
    - buspirone
  - Second-line pharmacologic therapies
    - TCAs
    - pregabalin
    - quetiapine
    - hydroxyzine
  - Third-line pharmacologic therapies
    - Monoamine oxidase inhibitors (MAOIs)
  - The above therapies can be augmented with the addition of BZDs such as alprazolam, clonazepam, diazepam, and lorazepam.
- World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders *(Bandelow et al 2012)*
  - GAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, paroxetine, and sertraline)
        - SNRIs (venlafaxine, duloxetine)
        - pregabalin
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - Imipramine is recommended as second-line therapy
      - BZDs (alprazolam, diazepam) are recommended for patients without a history of dependency
      - Hydroxyzine may be an effective option, although it can cause sedation
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-refractory GAD patients, augmentation of SSRI treatment with atypical antipsychotics (risperidone or olanzapine) may be used.
  - SAD
    - Recommendations, grade 1 (full evidence from controlled studies and good risk-to-benefit ratio)
      - First-line therapy
        - SSRIs (escitalopram, fluvoxamine, paroxetine, and sertraline)
        - venlafaxine
    - Recommendations, grade 2 (full evidence from controlled studies and moderate risk-to-benefit ratio)
      - The MAOI phenelzine is effective but less well tolerated than other antidepressants.
    - Recommendations, grade 3 (limited positive evidence from controlled studies)
      - In treatment-resistant cases, BZDs (clonazepam) may be used in patients without a history of dependency.
    - Recommendations, grade 4 (evidence from uncontrolled studies)
      - In treatment-resistant cases, the addition of buspirone to an SSRI was effective according to an open study.
- American Psychiatric Association practice guideline for the treatment of patients with panic disorder (second edition) *(Stein et al 2009)*
  - SSRIs, SNRIs, TCAs, and BZDs appear roughly comparable with regard to efficacy for panic disorder; however, SSRIs and SNRIs are recommended as first-line agents due to their relatively favorable safety profile.
  - BZDs may be used adjunctively with antidepressants to treat residual anxiety. BZDs may also be used as monotherapy or in combination with antidepressants for patients who are experiencing distressing symptoms that require rapid symptom control.
  - TCAs should be avoided in patients with acute narrow angle glaucoma or clinically significant prostatic hypertrophy. They may also increase the risk of falls in the elderly.

Insomnia

- American Academy of Sleep Medicine (AASM) Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults *(Sateia et al 2017)*
  - Recommendations for the treatment of sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended:
      - doxepin (low quality of evidence)
      - suvorexant (low quality of evidence)
    - The pharmacologic agents that are not recommended:
      - melatonin (very low quality of evidence)
      - tiagabine (low quality of evidence)
      - trazodone (moderate quality of evidence)
      - tryptophan (high quality of evidence)
      - valerian (low quality of evidence)
  - Recommendations for sleep onset and sleep maintenance insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended:
      - eszopiclone (very low quality of evidence)
      - temazepam (moderate quality of evidence)
      - zolpidem (very low quality of evidence)
    - The pharmacologic agent that is not recommended:
      - diphenhydramine (low quality of evidence)
  - Recommendations for sleep onset insomnia (vs. no treatment) in adults (all recommendations listed are considered of weak strength with varying qualities of evidence as noted below)
    - The pharmacologic agents that are recommended include:
      - ramelteon (very low quality of evidence)
      - triazolam (high quality of evidence)
      - zaleplon (low quality of evidence)
    - The pharmacologic agents that are not recommended:
      - melatonin (very low quality of evidence)
      - tiagabine (very low quality of evidence)
      - trazodone (moderate quality of evidence)
      - tryptophan (high quality of evidence)
      - valerian (low quality of evidence)
- American College of Physicians (ACP) Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guide *(Qaseem et al 2016)*
  - ACP recommends that all adults receive cognitive behavioral therapy for insomnia as the initial treatment for chronic insomnia disorder (Grade: strong recommendation, moderate-quality evidence).
  - ACP also recommends collaboration with the patient to determine whether a pharmacologic therapy should be initiated (Grade: weak recommendation, low-quality evidence).
    - Low-quality evidence shows that both eszopiclone and zolpidem improved global outcomes in the general population, and low- to moderate-quality evidence shows that eszopiclone, zolpidem, and doxepin improved sleep outcomes, such as sleep onset latency, TST, and WASO.
    - Moderate-quality evidence shows that suvorexant improved treatment response and sleep outcomes in mixed general and adult populations.
    - Low-quality evidence shows no statistically significant difference between ramelteon and placebo for sleep outcomes in the general population.
    - In older adults, low-quality evidence shows that eszopiclone improved global and sleep outcomes and both zolpidem and ramelteon decreased sleep onset latency.
    - Moderate-quality evidence shows that doxepin improved Insomnia Severity Index (ISI) scores, and low- to moderate-quality evidence shows that it improved sleep outcomes.
    - BZDs and melatonin were not included in these guidelines.
    - No one sedative hypnotic was recommended over another, due to insufficient evidence.

- Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (*VA/DoD 2019*)
  - The VA/DoD guideline recommends cognitive behavioral therapy (strong recommendation) and suggests brief behavioral therapy (weak recommendation) for chronic insomnia disorder. Cognitive behavioral therapy should be the first-line treatment over pharmacotherapy (weak recommendation).
  - Low-dose doxepin (ie, 3 mg or 6 mg) or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) are the recommended pharmacotherapies for short-course treatment of chronic insomnia disorder (weak recommendation).
  - The guideline recommends against using BZDs and trazodone for treating chronic insomnia disorder (weak recommendation).
  - The evidence remains insufficient to make recommendations regarding ramelteon or suvorexant for chronic insomnia disorder.

SAFETY SUMMARY

Contraindications

- MAOIs are contraindicated for concomitant use with buspirone and doxepin (or within 14 days of discontinuing an MAOI).
- Doxepin is contraindicated in patients with untreated narrow angle glaucoma or severe urinary retention.
- Suvorexant and lemborexant are contraindicated in patients with narcolepsy.
- Alprazolam products, estazolam, and triazolam are contraindicated with ketoconazole or itraconazole. Triazolam is also contraindicated with nefazodone and protease inhibitors.
- Alprazolam ODT, clonazepam, clorazepate, diazepam, and lorazepam are contraindicated in patients with acute narrow angle glaucoma.
- Clonazepam is contraindicated in patients with significant liver disease.
- Diazepam is contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea.
- Quazepam is contraindicated in patients with sleep apnea or chronic pulmonary insufficiency.
- Zolpidem products, eszopiclone, and zaleplon are contraindicated in patients with a prior history of complex sleep behaviors.

Warnings/Precautions

- Boxed warnings
  - BZDs carry a boxed warning for concomitant use with opioids, as it may result in profound sedation, respiratory depression, coma, and death.
  - Zolpidem products, eszopiclone, and zaleplon carry a boxed warning for complex sleep behaviors such as sleep-walking, sleep-driving, and other activities, which may lead to serious injuries, including death.
    - On April 30, 2019, the FDA mandated the addition of a boxed warning based on 66 cases of complex sleep behaviors with eszopiclone, zaleplon, or zolpidem leading to serious injuries, including death in 20 cases *(FDA Drug Safety Communication 2019)*.
- Daytime somnolence, sleep-walking, nighttime “sleep-driving,” and depression are listed as warnings for the majority of BZDs and non-BZDs in this review.
- Withdrawal effects can be observed after continuous long-term therapy with BZDs. Abrupt withdrawal or discontinuation should be avoided.
  - Withdrawal effects are mainly anxiety symptoms, but can also include autonomic instability (eg, diaphoresis, increased heart rate), insomnia, and sensory hypersensitivity. The most serious withdrawal effects are seizures and delirium tremens, which can occur with abrupt discontinuation.
- Severe anaphylaxis/anaphylactoid reactions (angioedema) have been reported with eszopiclone, flurazepam, quazepam, ramelteon, temazepam, zaleplon, and zolpidem.
- Worsening of symptoms of depression is considered a warning with most BZDs, doxepin, eszopiclone, zaleplon, zolpidem, lemborexant, and suvorexant.
- Pregnancy
  - All BZDs are considered highly teratogenic, especially during the first trimester.
  - Zolpidem use during the third trimester may lead to respiratory depression and sedation in neonates.

- Ramelteon shows a lack of a drug-associated risk for maternal and fetal outcomes based on postmarketing reports.
- Using meprobamate during the first trimester may lead to congenital malformations, and thus, meprobamate should be avoided during pregnancy.
- Other non-BZDs have not been studied in pregnant women and lack information on maternal or fetal outcomes in humans.

- Elderly
  - BZDs should be used cautiously in the elderly, ie, the lowest possible dose with slow dose up-titration should be utilized. Additionally, BZDs with a short half-life (eg, oxazepam) are preferred over those with a long half-life in the elderly patient population *(Gliatto 2000)*.
  - Zolpidem increases the risk of dizziness, drowsiness, and diarrhea in elderly patients.
  - Elderly patients have a 2-fold exposure to tasimelteon compared with younger patients.
  - With the non-BZDs, differences in the reported AEs between elderly and younger patients were not noted; however, older patients may be at a higher risk for drowsiness, and consequently, falls.

AEs

- Drowsiness, sedation, fatigue, cognitive impairment, and muscle weakness are the most frequent AEs with BZD use. Rare AEs include bradycardia, hypotension, rash, urticaria, blurred vision, diplopia, flushing, constipation, nausea, vomiting, change in libido, hepatic dysfunction, and abdominal pain.
- BZD use can lead to physiological dependence and tolerance, especially at higher doses and/or when given for a long duration. Treatment with BZDs should be limited to short-term use whenever possible. All BZDs are Schedule IV controlled substances.
- Somnolence/sedation and other central nervous system (CNS)-related AEs have also been reported with the non-BZD sedative hypnotics.

Drug Interactions

- In general, concomitant use of alcohol and other CNS depressants can increase the risk of CNS depression.
- The concomitant use of BZDs and opioids increases the risk of respiratory depression.
- Most BZDs (except lorazepam, oxazepam, and temazepam) are metabolized to some extent by cytochrome P450 (CYP) 3A4. Inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) can increase the risk of toxicity while inducers of CYP3A4 (eg, rifampin) can decrease their effectiveness.
- With the non-BZDs (buspirone, ramelteon, lemborexant, suvorexant, zolpidem), there can be an increased toxicity risk when administered concomitantly with CYP3A4 inhibitors. The efficacy of buspirone, eszopiclone, lemborexant, suvorexant, ramelteon, tasimelteon, zaleplon, and zolpidem may be reduced when these agents are co-administered with CYP3A4 inducers (particularly with rifampin when administered with eszopiclone or ramelteon). Lemborexant may decrease the levels of CYP2B6 substrates (eg, methadone, bupropion).

Recalls

- On October 25, 2019, Mylan voluntarily recalled 1 lot of alprazolam tablets (lot number 8082708) due to the potential presence of foreign substances that may lead to infection *(Mylan Pharmaceuticals 2019)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
BZDs				
Alprazolam products				
alprazolam	tablets, oral concentrate, orally disintegrating tablets	Oral	3 times daily	A lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xanax XR	Extended-release tablets	Oral	Once daily	Administer in the morning; a lower starting dose recommended for elderly, patients with advanced liver disease, and patients with a debilitating disease
Other BZDs				
chlordiazepoxide	Capsules	Oral	2 to 4 times daily	
clonazepam	Tablets	Oral	Twice daily	
clorazepate	Tablets	Oral	In divided doses or a single dose at bedtime	
diazepam	Tablets, oral concentrate, oral solution, injection	Oral, IV	2 to 4 times daily	
estazolam	Tablets	Oral	At bedtime	
flurazepam	Capsules	Oral	Before retiring	A lower dose is recommended for women, since they clear flurazepam from the body at a lower rate than men
lorazepam	Tablets, oral concentrate, injection	Oral, IV	2 to 3 times daily for anxiety or a single dose at bedtime for insomnia	
oxazepam	Capsules	Oral	3 to 4 times daily	
temazepam	Capsules	Oral	Before retiring	
triazolam	Tablets	Oral	Before bedtime	
quazepam	Tablets	Oral	At bedtime	
Non-BZDs				
buspirone	Tablets	Oral	Twice daily	Not recommended in patients with severe renal or hepatic impairment
doxepin	Tablets	Oral	Within 30 minutes of bedtime	A lower starting dose is recommended in the elderly
eszopiclone	Tablets	Oral	Immediately before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening	Do not exceed 2 mg in patients with severe hepatic impairment
lemborexant	Tablets	Oral	Immediately before bedtime, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment
meprobamate	Tablets	Oral	3 to 4 times daily	Not recommended in children < 6 years of age
ramelteon	Tablets	Oral	Within 30 minutes of bedtime	Not recommended in patients with severe hepatic impairment
suvorexant	Tablets	Oral	Within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening	Not recommended in patients with severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
tasimelteon	Capsules	Oral	Before bedtime, at the same time every night	Not recommended in patients with severe hepatic impairment
zaleplon	Capsules	Oral	Immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep	Not recommended in patients with severe hepatic impairment
zolpidem products				
Edluar	Tablets	SL	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Intermezzo	Tablets	SL	Should be administered when patient wakes in the middle of the night, but has at least 4 hours of bedtime remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Zolpimist	Oral spray	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien	Tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men
Ambien CR	Extended-release tablets	Oral	Immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening	A lower dose is recommended for women than for men, since they clear zolpidem from the body at a lower rate than men

Abbreviations: IV = intravenous; SL = sublingual
See the current prescribing information for full details

CONCLUSION

- No specific sedative hypnotic in this review is considered preferable to the others, as each has been shown to have positive effects on sleep latency, TST, and/or WASO in placebo-controlled trials.
- Individual patients may respond differently to these medications and therapy selection, therefore, should be based on consideration of the patient's specific symptom pattern, patient preferences, comorbid disease states, concurrent medications, and the side effect profile for each option *(Schutte-Rodin et al 2008)*.
- Depending on the patient's specific complaint of sleep initiation or sleep maintenance, consideration should be given to the pharmacokinetic parameters of the available hypnotics. Agents with a longer half-life may be preferred in those with sleep maintenance issues, while agents with a shorter time to maximum concentration may be preferred in patients with sleep initiation complaints. If a patient does not respond to the initial agent, a different agent within the same class is appropriate after evaluating the patient's response to the first agent *(Schutte-Rodin et al 2008)*.
- Tasimelteon is the only FDA-approved prescription product with proven efficacy for the treatment of Non-24 in totally blind patients.
- The recommended treatments for GAD include cognitive-behavioral therapy, applied relaxation, and preferred medications such as SSRIs and SNRIs *(Baldwin et al 2018)*.
- Although numerous meta-analyses have been conducted with the anxiolytic and sedative hypnotic classes, they are limited by lack of availability of high quality evidence and considerable variability in design and methodology across clinical trials *(Sateia et al 2017)*.

- The 2019 VA/DoD guideline recommends low-dose doxepin or non-BZD benzodiazepine receptor agonists (ie, zolpidem, zaleplon, eszopiclone) for short-course treatment of chronic insomnia disorder *(VA/DoD 2019)*.
- All of the BZDs and many of the non-BZD agents are Schedule IV controlled substances due to their propensity to cause physiological dependence. Withdrawal effects can be observed after continuous long-term therapy with many of these agents; therefore, abrupt withdrawal or discontinuation should be avoided.

REFERENCES

- Alprazolam ODT [package insert], Parsippany, NJ: Actavis Pharma, Inc; November 2019.
- Alprazolam Intensol [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp; March 2017.
- Ambien [package insert], Bridgewater, NJ: Sanofi-Aventis; August 2019.
- Ambien CR [package insert], Bridgewater, NJ: Sanofi-Aventis; August 2019.
- Ativan [package insert], Bridgewater, NJ: Valeant Pharmaceuticals LLC; October 2018.
- Baldwin D, Polkinghorn C. Evidence-based pharmacotherapy of generalized anxiety disorder. *Int J Neuropsychopharmacol.* 2005;8(2):293-302.
- Baldwin D, Stein MB, Hermann R. Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis. UpToDate Web site. www.uptodate.com. Updated April 3, 2018. Accessed April 1, 2020.
- Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind, D. Efficacy of treatments for anxiety: a meta-analysis. *Int Clin Psychopharmacol.* 2015;30(4):183-192.
- Bandelow B, Sher L, Bunevicius R,et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84.
- Belsomra [package insert], Whitehouse Station, NJ: Merck & Co.; March 2020.
- Breilmann J, Girlanda F, Guaiana G, et al. Benzodiazepines versus placebo for panic disorder in adults. *Cochrane Database Syst Rev*. 2019;3:CD010677. doi: 10.1002/14651858.CD010677.pub2.
- Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007; 22(9):1335-50.
- Buspirone [package insert], Bridgewater, NJ: Amneal Pharmaceuticals LLC; April 2017.
- Chlordiazepoxide [package insert], North Wales, PA: Teva Pharmaceuticals USA, Inc; August 2016.
- Anxiety disorders. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. http://dsm.psychiatryonline.org. PsychiatryOnline Web site. Accessed April 1, 2020.
- Dayvigo [package insert], Woodcliff Lake, NJ: Eisai, Inc. December 2019.
- Diazepam Intensol [package insert], Eatontown, NJ: West-Ward Pharmaceuticals Corp; May 2016.
- Doral [package insert], Atlanta, GA: Galt Pharmaceuticals LLC; December 2019.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 1, 2020.
- Edluar [package insert], Somerset, NJ: Meda Pharmaceutics, Inc.; August 2019.
- Estazolam [package insert], Parsipanny, NJ: Actavis Pharma, Inc.; October 2019.
- FDA drug safety communication: FDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. US Food and Drug Administration Web site. Updated May 14, 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia. Accessed April 1, 2020.
- Flurazepam [package insert], Morgantown, WV: Mylan Pharmaceutics, Inc.; December 2018.
- Generalized anxiety disorder. NIH/NIMH Web site. Updated November 2017. https://www.nimh.nih.gov/health/statistics/prevalence/generalized-anxiety-disorder-among-adults.shtml. Accessed April 1, 2020.
- Gliatto MF. Generalized Anxiety Disorder. *Am Fam Physician*. 2000;62(7):1591-1600.
- Halcion [package insert], New York, NY: Pharmacia and Upjohn Company; October 2019.
- Hetlioz [package insert], Washington, DC: Vanda Pharmaceutics, Inc.; October 2019.
- Huedo-Medina TB, Kirsch I, Middlemass J et al. Effectiveness of non-benzodiazepine hypnotics in the treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ*. 2012;345:e8343.
- Intermezzo [package insert], Stamford, CT: Purdue Pharma; August 2019.
- Klonopin [package insert], South San Francisco, CA: Genentech USA Inc; October 2017.
- Kong F, Liu G, Xu J. Pharmacological agents for improving sleep quality at high altitude: a systematic review and meta-analysis of randomized controlled trials. *Sleep Med*. 2018;51:105-114. doi: 10.1016/j.sleep.2018.06.017.
- Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. *Sleep Med Rev*. 2017;35:1-7. doi: 10.1016/j.smrv.2016.09.004.
- Locke AB, Kirst N, Shultz C. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician* 2015;91(9):617-624.
- Lockley SW, Dressman MA, Licamele L, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386(10005):1754-64
- Lorazepam Intensol [package insert], Branchburg, NJ: Amneal Pharmaceuticals LLC; September 2019.
- Lunesta [package insert], Marlborough, MA: Sunovian Pharmaceutics, Inc.; August 2019.
- Meprobamate [package insert], Eatontown, NJ: Heritage Pharmaceuticals, Inc,; July 2016.
- Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2014;13:461-471.
- Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol*. 2005;25(2):141-150.

- Mylan Pharmaceuticals initiates voluntary nationwide recall of one lot of alprazolam tablets, USP C-IV 0.5 mg, due to the potential of foreign substance. Food and Drug Administration Web site. Updated October 26, 2019. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/mylan-pharmaceuticals-initiates-voluntary-nationwide-recall-one-lot-alprazolam-tablets-usp-c-iv-05. Accessed April 1, 2020.
- Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF 3rd, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA*. 1997; 278(24):2170-7.
- 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 1, 2020.
- Oxazepam [package insert], Parsippany, NJ: Actavis Pharma, Inc.; September 2016.
- Restoril [package insert], St. Louis, MO: Mallinckrodt Pharmaceutics, Inc.; December 2018.
- Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. *JAMA Netw Open*. 2019 Dec 2;2(12):e1918254. doi: 10.1001/jamanetworkopen.2019.18254.
- Rozerem [package insert], Deerfield, IL: Takeda Pharmaceutics, Inc.; December 2018.
- Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guidelines for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(2):307-349.
- Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
- Silenor [package insert], Morristown, NJ: Currax Pharmaceuticals LLC; August 2019.
- Sonata [package insert], New York, NY: Pfizer, Inc.; August 2019.
- Stein MB, Goin MK, Pollack MH et al. American Psychiatric Association practice guideline for the treatment of patients with panic disorder. 2009. Psychiatry Online Web site. https://psychiatryonline.org/guidelines. Accessed on April 1, 2020.
- Qaseem A, Kangsara D, Forceia MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165:125-133.
- Tranxene-T [package insert], Lebanon, NJ: Recordati Rare Disease, Inc.; May 2018.
- Valium [package insert], Little Falls, NJ: Roche Laboratories Inc; June 2017.
- Veteran's Affairs/Department of Defense (VA/DoD) clinical practice guidelines - the management of chronic insomnia disorder and obstructive sleep apnea. Department of Veterans Affairs Web site. October 2019. https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp. Accessed April 1, 2020.
- Winkler A, Doering B K. Drug treatment of primary insomnia: A meta-analysis of polysomnographic randomized controlled trials. *CNS Drugs*. 2014:28:799–816.
- Xanax [package insert], New York, NY: Pharmacia and Upjohn Company; January 2017.
- Xanax XR [package insert], New York, NY: Pharmacia and Upjohn Company; December 2016.
- Zolpimist [package insert], Englewood, CO: Aytu BioScience, Inc.; August 2019.

Publication Date: May 4, 2020

Optum

Prior Authorization Guideline

Guideline Name: ~~Respiratory Monoclonal Antibody Agents~~
Respiratory and Allergy Biologics

1. Criteria

Product Name: **Cinqair**	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

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

AND

2 - The recipient must have a diagnosis of severe eosinophilic-phenotype asthma

AND

3 - The recipient is 18 years of age or older

AND

4 - The prescriber must be either a pulmonologist or allergist/immunologist

AND

5 - The recipient must be uncontrolled on current therapy including high dose corticosteroid and/or on a secondary asthma inhaler

AND

6 - There is documentation of the recipient's vaccination status

AND

7 - The requested dose is 3 mg/kg via intravenous infusion of 20 to 50 minutes every four weeks

Product Name: **Dupixent**	
Approval Length	6 Months for Asthma, 12 Months for Atopic Dermatitis and CRSwNP
Therapy Stage	Initial Authorization

Approval Criteria

1 - Diagnosis of moderate to severe atopic dermatitis and all of the following:

1.1 Prescribed by or in consultation with a dermatologist or allergist/immunologist

AND

1.2 One of the following:

1.2.1 Trial and failure, contraindication, or intolerance to one medium to high potency topical corticosteroid (e.g. betamethasone, tramcinolone)

OR

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

- Elidel (pimecrolimus) topical cream
- Tacrolimus topical ointment

OR

2 - Diagnosis of moderate to severe asthma and all of the following:

2.1 Recipient is 6 years of age or older

AND

2.2 One of the following:

2.2.1 The recipient is currently dependent on oral corticosteroids for the treatment of asthma
- One or more asthma exacerbations requiring systemic corticosteroids within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

OR

2.2.2 All of the following:

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

AND

2.2.2.2 The recipient has one of the following:

- One or more asthma exacerbations requiring systematic corticosteroid within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

2.3 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

2.4 Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

OR

3 - Diagnosis of Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) and all of the following:

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

AND

3.2 The medication will not be used in combination with another agent for CRSwNP

AND

3.3 Prescribed by or in consultation with an allergist/immunologist

Product Name: **Dupixent**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Diagnosis of moderate to severe atopic dermatitis and all of the following:

1.1 Documentation of positive clinical response to Dupixent therapy

OR

2 - Diagnosis of moderate to severe eosinophilic asthma or oral corticosteroid-dependent asthma and all of the following:

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

AND

2.2 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

2.3 Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

OR

3 - Diagnosis of Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) and all of the following:

3.1 Documentation of a positive clinical response to therapy

AND

3.2 The medication will not be used in combination with another agent for CRSwNP

AND

3.3 Prescribed by or in consultation with an allergist/immunologist

Product Name: **Fasenra**	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

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

AND

2 - The recipient has a diagnosis of severe eosinophilic phenotype asthma

AND

3 - The recipient is 12 years of age or older

AND

4 - Recipient has one of the following:

- One or more asthma exacerbations requiring systemic corticosteroids within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

5 - Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

6 - Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

Product Name: **Fasenra**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

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

AND

2 - Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

3 - Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

Product Name: **Nucala**	
Approval Length	6 Months for Asthma, 12 Months for EGPA
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient has diagnosis of severe asthma and all of the following:

1.1 The asthma is an eosinophilic phenotype as defined by one of the following:

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

AND

1.2 Recipient has one of the following:

- One or more asthma exacerbations requiring systemic corticosteroid within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

1.3 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

1.4 Recipient is 6 years of age or older

AND

1.5 Prescribed by or in consultation with a pulmonologist or allergist/immunologist

OR

2 - The recipient has diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and all of the following:

2.1 The recipient's disease has relapsed or is refractory to standard of care therapy (i.e. corticosteroid treatment with or without immunosuppressive therapy)

AND

2.2 The recipient is currently receiving corticosteroid therapy

AND

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

- Pulmonologist
- Rheumatologist
- Allergist/Immunologist

Product Name: **Nucala**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient has diagnosis of severe eosinophilic-phenotype asthma and all of the following:

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

AND

1.2 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

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

OR

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

AND

1.3 Prescribed by or in consultation with a pulmonologist or allergist/immunologist

OR

2 - The recipient has diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and all of the following:

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

Product Name: **Xolair**	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

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

AND

2 - One of the following:

2.1 Diagnosis of moderate to severe persistent asthma and all of the following:

2.1.1 The recipient must be six years of age or older

AND

2.1.2 The recipient must have a history of a positive skin test or Radioallergosorbent (RAST) test to a perennial aeroallergen

AND

2.1.3 The prescriber must be either a pulmonologist or allergist/immunologist

AND

2.1.4 The recipient must have had an inadequate response, adverse reaction or contraindication to inhaled corticosteroids

AND

2.1.5 The recipient must have had an inadequate response, adverse reaction or contraindication to a leukotriene receptor antagonist

AND

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

AND

2.1.7 The recipient's current weight must be recorded (document weight)

AND

2.1.8 The requested dose is appropriate for the recipient's pre-treatment serum IgE and body weight (see Table 1 (pharmacist review required))

OR

2.2 Diagnosis of chronic idiopathic urticaria (CIU) and all of the following:

2.2.1 The recipient is 12 years of age or older

AND

2.2.2 The recipient must have had an inadequate response, adverse reaction, or contraindication to two different oral second-generation antihistamines

AND

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

AND

2.2.4 The prescriber must be one of the following, or there is documentation in the recipient's medical record that a consultation regarding diagnosis and treatment recommendations was done by one of the following:

- Allergist/immunologist
- Dermatologist
- Rheumatologist

AND

2.2.5 One of the following:

2.2.5.1 The request is for initiation of therapy and the dose will be 150 mg every four weeks

OR

2.2.5.2 The request is for initiation of therapy and the dose will be 300 mg every four weeks, and clinical rationale for starting therapy at 300 mg every four weeks has been provided (pharmacist review required)

OR

2.2.5.3 The request is for continuation of therapy and the dose will be 150 mg or 300 mg every four weeks

2.3 Diagnosis of nasal polyps and all of the following:

2.3.1 The recipient is 18 years of age or older

AND

2.3.2 The prescriber must be one of the following, or there is documentation in the recipient's medical record that a consultation regarding diagnosis and treatment recommendations was done by one of the following:

- Allergist/immunologist
- Dermatologist
- Rheumatologist

AND

2.3.3 The recipient must have had an inadequate response, adverse reaction, or contraindication to at least 2 months of therapy with an intranasal corticosteroid and had inadequate response

AND

2.3.4 One of the following:

2.3.4.1 The recipient will continue intranasal corticosteroid treatment along with omalizumab therapy

OR

2.3.4.2 The prescriber has provided valid medical rationale for not continuing intranasal corticosteroid treatment along with omalizumab therapy

OR

2.3.5 The request is for continuation of therapy and there is documentation of a positive clinical response to therapy (e.g., reduction in nasal polyps score [NPS; 0-8 scale], improvement in nasal congestion/obstruction score [NCS; 0-3 scale])

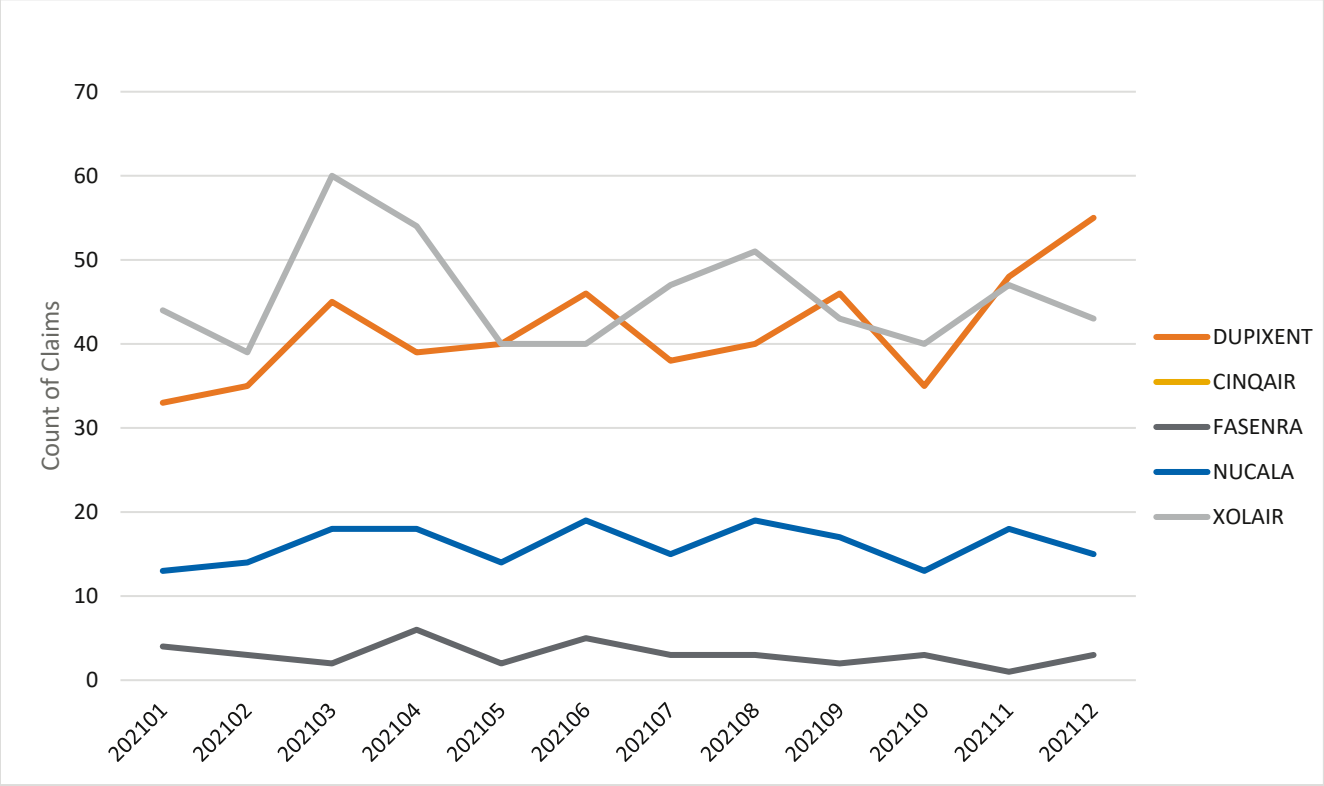
Nevada Medicaid

Utilization

Fee for Service

January 1, 2021 – December 31, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
CINQAIR	1	1	1	20
DUPIXENT	66	500	13,770	3,082
FASENRA	12	37	1,402	211
NUCALA	28	193	3,973	19,188
XOLAIR	70	548	11,286	6,245



INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages but most often starts during childhood. In 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.). The exact causes of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*Cloutier et al 2020, NHLBI 2007, Global Initiative for Asthma [GINA] 2021*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- Approximately 3.7% of asthma patients have severe disease and 17% have difficult-to-treat asthma. Severe asthma is defined as asthma that is uncontrolled despite adherence to maximal optimized high dose ICS/LABA treatment or asthma that requires high doses of ICS/LABA to remain controlled (*GINA 2021*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent GINA guideline on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level, and allergic triggers to asthma (*GINA 2021*).
- Chronic idiopathic urticaria (CIU), also called chronic spontaneous urticaria, is defined by the presence of hives on most days of the week for 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2021, Saini 2021*).
- CIU affects up to 1% of the general population in the U.S., and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2021*).
- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not

respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, dapsone, and omalizumab (*Khan 2021, Maurer et al 2013*).

- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Padmanabhan et al 2019).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Chronic rhinosinusitis with nasal polyposis (CRSwNP) has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact the quality of life. The majority of cases are idiopathic, but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and IL-13 *(Hopkins 2019)*.
- Common treatment options for CRSwNP include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms *(Hopkins 2019)*.
- Hypereosinophilic syndromes (HES) are disorders characterized by overproduction of eosinophils which causes organ damage (*Roufosse et al 2020a*). Treatment for idiopathic HES may include systemic glucocorticoids, imatinib, hydroxyurea, interferon alfa, alemtuzumab, and Janus kinase inhibitors (eg, tofacitinib and ruxolitinib). Additionally, mepolizumab was Food and Drug Administration (FDA)-approved for HES in 2020.
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through the release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
    - Nucala is also approved for the treatment of adult patients with EGPA, patients ≥ 12 years of age with HES, and as add-on therapy for inadequately controlled CRSwNP.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU and is indicated for add-on maintenance treatment of nasal polyps in adult patients with inadequate response to nasal corticosteroids.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for eosinophilic asthma and add-on therapy for inadequately controlled CRSwNP. Dupixent is also approved to treat moderate to severe atopic dermatitis; this indication is not discussed further in this review.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

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

(*Drugs@FDA 2021, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2021*)

INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients ≥ 12 years of age with severe asthma with an eosinophilic phenotype			✔		
Add-on maintenance treatment for patients ≥ 6 years of age with severe asthma with an eosinophilic phenotype				✔	
Add-on maintenance treatment for patients ≥ 6 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients ≥ 18 years of age with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	
Add-on maintenance treatment of nasal polyps for patients ≥ 18 years of age with an inadequate response to nasal corticosteroids					✔
The treatment of adults and adolescents ≥ 12 years of age with chronic idiopathic urticaria (CIU) who remain					✔

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
symptomatic despite H_1-antihistamine treatment.					
Add-on maintenance treatment in adult patients with inadequately controlled CRSwNP		✔		✔	
Treatment of adult and pediatric patients ≥ 12 years of age with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause				✔	

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

(*Prescribing information: Cinqair 2020, Dupixent 2021, Fasenra 2021, Nucala 2021, Xolair 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

OMALIZUMAB

Asthma

- The original FDA approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (p-value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors

concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who have established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit (*Ledford et al 2017*).

Chronic idiopathic urticaria (CIU)

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose-dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose-dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials and a 2020 meta-analysis of 9 trials, both comparing omalizumab with placebo (*Jia and He 2020, Rubini et al 2019*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; $p < 0.0001$). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

Nasal Polyps

- The efficacy and safety of omalizumab for the treatment of nasal polyps in adult patients with an inadequate response to intranasal corticosteroids were based on results from 2 randomized, multicenter, double-blind, placebo-controlled,

Phase 3 studies, POLYP 1 (n = 138) and POLYP 2 (n = 127) (*Gevaert et al 2020*). Patients were randomly assigned to omalizumab 75 to 600 mg SC every 2 or 4 weeks (based upon pretreatment serum total IgE level and body weight) or placebo for 24 weeks. All patients received background intranasal mometasone therapy. Results from both studies revealed that omalizumab was associated with a significantly greater improvement from baseline at week 24 in Nasal Polyp Score (NPS) and weekly average Nasal Congestion Score (NCS) as compared to placebo. In POLYP 1 and POLYP 2, the mean changes in NPS from baseline to week 24 for omalizumab compared to placebo were -1.08 vs 0.06 ($p < 0.0001$) and -0.9 vs -0.31 ($p = 0.014$), respectively, and mean changed in NCS from baseline were -0.89 vs -0.35 ($p = 0.0004$) and -0.7 vs -0.2 ($p = 0.0017$), respectively. Adverse events were similar between treatment groups.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 4 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017, Harrison et al 2021*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; $p = 0.096$). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; $p = 0.015$) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; $p = 0.049$) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; $p < 0.0001$) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; $p < 0.0001$). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; $p = 0.0018$) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; $p = 0.0188$). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORA Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2019a*).

- BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
- ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (p < 0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; p = 0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; p < 0.001).
- ANDHI was a randomized, multicenter, double-blind, placebo-controlled, Phase 3b study that assessed the effect of benralizumab in adults with severe eosinophilic asthma and at least 2 exacerbations in the previous year despite use of medium- to high-dose ICS plus another asthma controller (*Harrison et al 2021*). Patients were randomized to receive benralizumab 30 mg every 8 weeks (with the first 3 doses given 4 weeks apart; n = 427) or placebo (n = 229). Benralizumab significantly reduced annualized asthma exacerbation rate over the 24-week treatment period compared to placebo (RR, 0.51; 95% CI, 0.39 to 0.65; p < 0.0001).

- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA Phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; p < 0.0001). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; p < 0.0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; p < 0.00001) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration did not result in an increased incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; p = 0.96) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (p < 0.0001), 1.46 in the 250 mg mepolizumab group (p = 0.0005), and 1.15 in the 750 mg

mepolizumab group (p < 0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (p < 0.001), and 0.83 per patient per year in the SC mepolizumab group (p < 0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (p < 0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; p = 0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (p = 0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; p < 0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/μL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/μL. At a baseline count < 150 cells/μL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for the treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant

reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic granulomatosis with polyangiitis (EGPA)

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

Hypereosinophilic syndrome (HES)

- A 32-week, double-blind, placebo-controlled, multicenter, randomized controlled trial evaluated the efficacy and safety of mepolizumab in patients ≥ 12 years with HES (without an identifiable nonhematologic secondary cause) for at least 6 months *(Nucala prescribing information 2021, Roufosse et al 2020b)*. A total of 108 patients were assigned to mepolizumab 300 mg every 4 weeks (n = 54) or placebo (n = 54). Results demonstrated the following for mepolizumab and placebo groups, respectively:
  - Proportion of patients with ≥ 1 HES flare or withdrew from the trial: 28% vs 56% (OR, 0.28; 95% CI, 0.12 to 0.64; p = 0.002)
  - Adjusted mean rate of HES flares per year: 0.50 vs 1.46 (rate ratio, 0.34; 95% CI, 0.19 to 0.63; p < 0.001)
  - Probability of first HES flare by week 32: 26.3% vs 52.7% (hazard ratio, 0.34; 95% CI, 0.18 to 0.67; p = 0.002)

CRSwNP

- SYNAPSE, a 52-week, double-blind, randomized, placebo-controlled, multicenter trial, evaluated the efficacy and safety of mepolizumab in adult patients with CRSwNP. A total of 407 patients with recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard care treatment were enrolled. Patients were randomly assigned to receive 100 mg mepolizumab (n = 206) or placebo (n = 201) every 4 weeks. The total endoscopic nasal polyp score significantly improved from baseline with mepolizumab versus placebo (adjusted difference in medians, -0.73; 95% CI, -1.11 to -0.34; p < 0.0001). The nasal obstruction VAS score during weeks 49 to 52 also significantly improved (adjusted difference in medians, -3.14; 95% CI, -4.09 to -2.18; p < 0.0001). Adverse events related to study treatment occurred in 15% of the mepolizumab group and 9% of the placebo group (*Han et al 2021*).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al 2016*).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/μL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: RR, 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL;

95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
  - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/µL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/µL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/µL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
- An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer, and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
- A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with oral corticosteroid dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2020)*.

- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; p < 0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; p < 0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; p < 0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 randomized controlled trials (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83; 95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) *(Virchow et al 2020)*.

DUPILUMAB

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300/mm^3 was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo (p < 0.0001). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both p < 0.01) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both p < 0.001) *(Corren et al 2020)*.
- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered

from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).

- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; $p < 0.01$). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; $p < 0.01$). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; $p < 0.01$) (*Zayed et al 2018*).
- A randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of dupilumab in pediatric patients 6 to 11 years of age with moderate-to-severe asthma on a medium- or high-dose ICS and a second controller medication or high-dose ICS alone. In the 52-week trial, patients were randomized to receive dupilumab (n = 273) or placebo (n = 135) every other week. Dosing was dependent on body weight: patients < 30 kg received 100 mg every 2 weeks, those ≥ 30 kg received 200 mg every 2 weeks. The annualized rate of severe asthma exacerbation events during the study period was significantly reduced in the dupilumab group compared to placebo (rate ratio, 0.35; 95% CI, 0.22 to 0.56). Mean change from baseline in percent predicted FEV_1 was also significantly improved in the dupilumab group compared to placebo (least squares mean difference vs placebo, 5.32; 95% CI, 1.76 to 8.88). The efficacy of dupilumab 300 mg every 4 weeks in patients 6 to 11 years of age with body weight 15 to < 30 kg was extrapolated from efficacy of 100 mg every 2 weeks clinical trial with support from population pharmacokinetic analyses. The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo with the addition of helminth infections (*Dupixent prescribing information 2021*).

CRSwNP

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral CRSwNP (*Bachert et al 2019*). Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by least-squares mean differences in NPS (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13; 95% CI, -5.80 to -4.46, respectively). The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo.

COMPARATIVE REVIEWS

Asthma

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history, and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CI, 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.

  - Both treatments had broadly comparable effects on lung function and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019)*.
- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/µL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/µL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/µL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/µL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/µL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/µL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/µL *(Busse et al 2019b)*.
- A 2019 systematic review and network meta-analysis of 30 randomized controlled trials compared biologic therapies for treatment of type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the U.S. (lebrikizumab, tralokinumab, and tezepelumab) *(Edris et al 2019)*.
- In a 2020 meta-analysis including data from 3 trials (n = 2640), dupilumab and benralizumab were compared in patients with inadequately controlled asthma. While there were no significant differences in the annual exacerbation rates between both drugs in the overall population (RR, 0.83; 95% CI, 0.62 to 1.09) and in the subgroup with the blood eosinophil count <150 cells/µL (RR, 1.57; 95% CI, 0.73 to 2.82), dupilumab was superior to benralizumab for the subgroup with a blood eosinophil count of ≥ 300 cells/µL (RR, 0.58; 95% CI, 0.39 to 0.84) and ≥ 150 but < 300 cells/µL (RR, 0.51; 95% CI, 0.29 to 0.92). The incidence of adverse events was similar between groups (OR, 1.023; 95% CI, 0.688 to 1.526) (*Ando et al 2020*).
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018, Yan et al 2019).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score, and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2

tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. An increase in FEV_1, reduction in ACQ score, and increase in AQLQ score were observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).

- In a 2020 network meta-analysis including 9 studies, treatment rankings estimated that dupilumab was most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab. Similar to other indirect treatment comparisons, there were no within-group differences as related to the risk for asthma exacerbations (*Ramonell et al 2020*).

CRSwNP

- In a 2021 network meta-analysis including 9 randomized controlled trials, 4 different biologics (dupilumab [n = 3], omalizumab [n = 4], mepolizumab [n = 2]) and placebo were compared in patients with CRSwNP. Dupilumab was found to be the most efficacious in terms of nasal polyp score (NPS), Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and nasal congestion score (NCS) surface under the cumulative ranking curve (SUCRA) values of 0.900, 0.916, 1.000, and 0.807, respectively. Omalizumab ranked second in efficacy in SNOT-22, UPSIT, and NCS scores with SUCRA values of 0.606, 0.500, and 0.693, respectively. Mepolizumab had the highest risk of adverse events for SUCRA values of 0.746 (*Wu et al 2021*).

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients ≥ 12 years of age who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
  - A 2020 focused update of the 2007 NHLBI guidelines provided updated recommendations on limited topics for the clinical management of adolescents and adults with asthma, including intermittent ICSs, add-on therapy with long-acting muscarinic antagonists, fractional exhaled nitric oxide, indoor allergen mitigation and immunotherapy. Addition of the asthma biologics (eg, anti-IgE, anti-IL5, anti-IL5R, or anti-IL4/IL13) to therapy could be considered in steps 5 and 6 in the stepwise approach for management of asthma. However, the systematic reviews that informed the update did not include studies examining the role of asthma biologics, and therefore, the report did not contain specific recommendations for use of biologics in asthma.
- In 2021, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2021, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma were included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, medium dose ICS/formoterol with as needed low dose ICS/formoterol as the reliever therapy), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended

for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency, and patient preference (*GINA 2021*).
    - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma suggests the use of anti-IL-5 therapy as an add-on in adults with severe uncontrolled eosinophilic asthma or severe corticosteroid-dependent asthma. A blood eosinophil count of 150 cells/mcL or greater is suggested as a cut-point to guide initiation of anti-IL-5 therapy in adults with severe asthma and prior exacerbations. A blood eosinophil count of 260 cells/mcL or greater or an exhaled nitric oxide level of 19.5 parts per billion or greater may be used to identify adolescents and adults with severe allergic asthma who are likely to benefit from anti-IgE treatment. Dupilumab is suggested for adults with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (*Holguin et al 2020*).

Chronic idiopathic urticaria (CIU)

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

Eosinophilic granulomatosis with polyangiitis (EGPA)

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Padmanabhan et al 2019*).

CRSwNP

- Treatment of CRSwNP is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; the International Forum of Allergy & Rhinology; and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).
- Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms (*Orlandi*

et al 2016, Peters et al 2014, Rosenfeld et al 2015). While not approved at the time of writing, some guidelines acknowledged the demonstration of benefit with IL-5 antagonists (*Orlandi et al 2016, Peters et al 2014*).

- In 2019, EUFOREA published an expert consensus focused on the use of biologics for CRSwNP with or without asthma. Per EUFOREA, biologics are indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); the need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).

Hypereosinophilic syndrome (HES)

- The World Health Organization (WHO) guidance on eosinophilic disorders have stated that identification of rearranged *PDGFRA* or *PDGFRB* is important in the management of eosinophilic disorders as those variants respond to imatinib (*Shomali and Gotlib 2019*). For patients with idiopathic HES (without imatinib-sensitive variants), corticosteroids are first-line therapy; second-line options include hydroxyurea, interferon-alfa, other cytotoxic chemotherapy agents, and hematopoietic stem cell transplantation. The WHO listed use of mepolizumab or benralizumab as an area of active investigation. The WHO guidance was published prior to the FDA approval of mepolizumab for HES.

SAFETY SUMMARY

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

Cinqair

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

Dupixent

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, erythema multiforme, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.

- Adverse reactions:
  - Asthma: the most common adverse reactions included injection site reactions, oropharyngeal pain, and eosinophilia.
    - The safety profile in patients 6 to 11 of age was similar to the safety profile from studies in adults and adolescents with the addition of helminth infections. Adverse reactions of helminth infections were reported in pediatric patients (5 cases of enterobiasis and 1 case of ascariasis) who participated in clinical studies.
  - CRSwNP: the most common adverse reactions included injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.

Fasenra

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

Nucala

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

Xolair

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Initiate Xolair in a healthcare setting and closely observe patients for an appropriate period of time after administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Selection of patients for self-administration of Xolair should be based on criteria to mitigate risk from anaphylaxis.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment. Approximately 60 to 70% of anaphylaxis cases have been reported to occur within the first 3 doses.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy for asthma or nasal polyps.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions:
  - Asthma: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain,

fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
    - Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
- CIU: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Nasal polyps: The most common adverse reactions (≥ 3% of patients) in clinical studies included headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	Single-use vials	IV	Every 4 weeks	• Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Cinqair should be administered by a healthcare professional by IV infusion over 20 to 50 minutes.
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Asthma: every other week In pediatric patients (6 to 11 years of age) weighing 15 kg to < 30 kg, dosing regimen for asthma can also include every 4 weeks. CRSwNP: every other week	• Safety and efficacy in patients < 6 years of age (asthma) and < 18 years of age (CRSwNP) have not been established. • Dupixent may be administered by a healthcare professional or self-administered via pre-filled syringe or pen.
Fasenra (benralizumab)	Single-dose pre-filled syringe, single-dose pre-filled pen (autoinjector)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	Single-dose vial for reconstitution, single-dose pre-filled pen (autoinjector), single-dose prefilled syringe	SC	Asthma: every 4 weeks EGPA: every 4 weeks HES: every 4 weeks CRSwNP: every 4 weeks	• Safety and efficacy in pediatric patients < 6 years (asthma), < 18 years (EGPA), < 12 years (HES) of age, and < 18 years of age (CRSwNP) have not been established. • Nucala may be administered by a healthcare professional or self-administered via an autoinjector or pre-filled syringe.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xolair (omalizumab)	Single-dose vial for reconstitution, single-dose prefilled syringe	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks Nasal polyps: Every 2 or 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age (asthma), < 12 years of age (CIU), < 18 years of age (nasal polyps) have not been established. • Xolair should be initiated in a healthcare setting: once therapy has been safely established, Xolair may be administered by a healthcare professional or self-administered via a pre-filled syringe. • For allergic asthma and nasal polyps, dose and frequency are determined by serum total IgE level (measured before the start of treatment) and body weight. • Dosing in CIU is not dependent on serum IgE level or body weight.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients ≥ 6 years of age with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
  - Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be initiated in a healthcare setting. Once therapy has been safely established, select patients may be able to self-administer Xolair using a pre-filled syringe.
  - Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
  - Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*Cloutier et al 2020, GINA 2021, NHLBI 2007*). Based on a limited place in therapy, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA approval for the treatment of adults and adolescents (≥ 12 years of age) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients.
  - In patients with CIU, Xolair is administered at 150 or 300 mg SC every 4 weeks.
  - Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).

- Xolair was approved as add-on maintenance treatment for nasal polyps in adult patients with an inadequate response to nasal corticosteroids, based on results from 2 identical, randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies [POLYP 1 and POLYP 2] (*Gevaert et al 2020*). Results from both studies revealed that Xolair was associated with a significantly greater improvement from baseline at week 24 in NPS and weekly average NCS as compared to placebo. Adverse events were similar between groups.
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*).
  - The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe asthma and should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids (*GINA 2021*).
- Dupixent is an IL-4/IL-13 antagonist approved for the treatment of patients ≥ 6 years of age with moderate-to-severe asthma of the eosinophilic type or dependent on oral corticosteroids, and as an add-on treatment in adults with inadequately controlled CRSwNP.
  - According to GINA guidelines, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids.
- Dupixent was approved for CRSwNP after the publication of several guidelines, although some acknowledged the potential role for biologic therapies (*Orlandi et al 2016, Peters et al 2014).*
  - In a 2019 EUFOREA expert consensus publication focused on the use of biologics for CRSwNP with or without asthma, biologics were indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).
- Nucala is the only antiasthmatic monoclonal antibody approved for the treatment of adult patients with EGPA and patients ≥ 12 years of age with HES. Nucala is also approved as an add-on treatment in adults with inadequately controlled CRSwNP.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala.
  - A systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events (*Farne et al 2017*).
  - One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab; other analyses found that dupilumab, mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Iftikhar et al 2018, Edris et al 2019, Ando et al 2020, Ramonell et al 2020*).
  - Treatment rankings in a 2020 network meta-analysis estimate that dupilumab is most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab (*Ramonell et al 2020*).
- Compared to Nucala and Fasenra, Cinqair has various limitations, including an indication for patients ≥ 18 years of age (vs ≥ 6 and 12 years of age with Nucala and Fasenra, respectively), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 6 years of age with moderate-to-severe asthma.
- Subcutaneous autoinjector formulations are available for Dupixent, Fasenra, and Nucala.

REFERENCES

- Ando K, Tanaka A, Sagara H. Comparative efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma: a systematic review. *Int J Mol Sci*. 2020;21(3):889. doi:10.3390/ijms21030889

- Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials *Lancet*. 2019;394(10209):1638-1650. doi: 10.1016/s0140-6736(19)31881-1.
- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189-1197.
- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
- Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789-798.
- Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
- Bourdin A, Husereau D, Molinari N, et al. Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. *Eur Respir J.* 2018;52(5). doi: 10.1183/13993003.01393-2018.
- Buhl R, Solèr M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J*. 2002;20(1):73-78.
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-90.
- Busse WW, Bleecker ER, FitzGerald JM, et al; BORA study investigators. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019a;7(1):46-59. doi: 10.1016/S2213-2600(18)30406-5.
- Busse W, Chupp G, Nagase H, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. *J Allergy Clin Immunol*. 2019b;143(1):190-200.e20. doi: 10.1016/j.jaci.2018.08.031.
- Casale TB, Pacou M, Mesana L, et al. Reslizumab compared with benralizumab in patients with eosinophilic asthma: a systematic literature review and network meta-analysis. *J Allergy Clin Immunol Pract*. 2019;7(1):122-130.e1. doi: 10.1016/j.jaip.2018.08.036.
- Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med*. 2014;2(11):879-890.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
- Centers for Disease Control and Prevention. Asthma: Most Recent National Asthma Data. 2019. Updated March 2021. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed November 19, 2021.
- Cinqair [package insert], information. Frazer, PA: Teva Pharmaceutical Industries Ltd.; June 2020.
- Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. *JAMA*. 2020;324(22):2301-2317. doi: 10.1001/jama.2020.21974.
- Cockle SM, Stynes G, Gunsoy NB, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. *Respir Med*. 2017;123:140-148.
- Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526. doi: 10.1016/j.jaip.2019.08.050.
- Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
- Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 19, 2021.
- Dupixent [package insert], Bridgewater, NJ: Sanofi-Aventis US, LLC and Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; October 2021.
- Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res*. 2019;20(1):179. doi: 10.1186/s12931-019-1138-3.
- Eisner MD, Zazzali JL, Miller MK, et al. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS study. *J Asthma*. 2012;49:642-648.
- Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017 Sep 21;9:CD010834.
- Fasenra [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals.; February 2021.
- Ferguson GT, Fitzgerald JM, Beecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):568-576.
- FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6(1):51-64.
- Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
- Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019;74(12):2312-2319. doi:10.1111/all.13875
- Food and Drug Administration press release. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair, including describing slightly higher risk of heart and brain adverse events. September 26, 2014. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-asthma-drug-xolair-omalizumab-including. Accessed November 19, 2021.

- Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595-605. doi: 10.1016/j.jaci.2020.05.032.
- GlaxoSmithKline. Nucala is the first biologic approved in the US for six to 11-year-old children with severe eosinophilic asthma. September 12, 2019. GlaxoSmithKline Web site. https://www.gsk.com/en-gb/media/press-releases/nucala-is-the-first-biologic-approved-in-the-us-for-six-to-11-year-old-children-with-severe-eosinophilic-asthma/. Accessed November 19, 2021.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2021. www.ginasthma.org. Accessed November 19, 2021.
- Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015;26(7):545-553.
- Gupta A, Ikeda M, Geng B, et al. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol*. 2019b;144(5):1336-1342.e7. doi: 10.1016/j.jaci.2019.08.005.
- Gupta A, Pouliquen I, Austin D, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. *Pediatr Pulmonol.* 2019a;54(12):1957-1967. doi: 10.1002/ppul.24508.
- Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141-1153. doi:10.1016/S2213-2600(21)00097-7.
- Harrison TW, Chanez P, Menzella F, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med.* 2021;9(3):260-274. doi: 10.1016/S2213-2600(20)30414-8.
- Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis. *Eur Clin Respir J*. 2018;5(1):1536097. doi: 10.1080/20018525.2018.1536097.
- Holgate S, Bousquet J, Wenzel S, et al. Efficacy of omalizumab, an antiimmunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin*. 2001;17(4):233-240.
- Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632-8.
- Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55(1). pii: 1900588. doi: 10.1183/13993003.00588-2019.
- Hopkins C. Chronic Rhinosinusitis with Nasal Polyps. *N Engl J Med*. 2019;381(1):55-63. doi: 10.1056/NEJMcp1800215.
- Iftikhar IH, Schimmel M, Bender W, et al. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung.* 2018;196(5):517-530. doi: 10.1007/s00408-018-0151-5.
- Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma. *J Allergy Clin Immunol*. 2017;139(5):1489-1495.e5.
- Jia HX, He YL. Efficacy and safety of omalizumab for chronic spontaneous urticaria: a systematic review and meta-analysis of randomized controlled trials. *Am J Ther*. 2020. doi:10.1097/MJT.0000000000000912
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101-9.
- Khan DA. Chronic spontaneous urticaria: treatment of refractory symptoms. UpToDate Web site. https://www.uptodate.com. Updated January 21, 2021. Accessed November 19, 2021.
- Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol*. 2018;143(5):1742-1751. doi: 10.1016/j.jaci.2018.09.033.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-6.
- Lanier BQ, Corren J, Lumry W, et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91(2):154-9.
- Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.e2.
- Li J, Wang F, Lin C, et al. The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis. *J Asthma.* 2017;54(3):300-307.
- Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560-567.
- Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38(9):2058-2070.
- Maurer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2018;141(3):1138-1139.e7.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
- Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract.* 2017;5(6):1572-1581.e3. doi: 10.1016/j.jaip.2017.08.024.
- Nachef Z, Krishnan A, Mashtare T, Zhuang T, Mador MJ. Omalizumab versus mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: a network meta-analysis. *J Asthma*. 2018;55(1):89-100.
- Nair P, Bardin P, Humbert M, et al. Efficacy of intravenous reslizumab in oral corticosteroid-dependent asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):555-564. doi: 10.1016/j.jaip.2019.09.036.
- Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
- National Heart, Lung, and Blood Institute: Asthma. NHLBI Web site. https://www.nhlbi.nih.gov/health-topics/asthma. Accessed November 19, 2021.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed November 19, 2021.
- Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev. 2014 Jan 13;(1):CD003559.

- Nucala [package insert], Philadelphia, PA: GlaxoSmithKline LLC; July 2021.
- Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6 Suppl 1:S22-209. doi: 10.1002/alr.21695.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-1207.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
- Padmanabhan A, Connelly-smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. *J Clin Apher*. 2019;34(3):171-354. doi: 10.1002/jca.21705.
- Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Expert Rev Clin Immunol;*2016;12(10):1059-1067.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651-659.
- Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol.* 2014;113(4):347-85. doi: 10.1016/j.anai.2014.07.025.
- Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2015;45(3):547-565.
- Purple Book: Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Food and Drug Administration Web site. https://www.fda.gov/drugs/biosimilars/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or. Accessed November 19, 2021.
- Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.
- Ramonell RP, Iftikhar IH. Effect of anti-IL5, anti-IL5r, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. *Lung*. 2020;198(1):95-103. doi:10.1007/s00408-019-00310-8
- Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28-35.
- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 Suppl):S1-S39. doi: 10.1177/0194599815572097.
- Roufosse F, Kahn JE, Rothenberg ME, et al; HES Mepolizumab study group. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020b;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037.
- Roufosse F, Klion AD, Weller PF. Hypereosinophilic syndromes: treatment. UpToDate Web site. www.uptodate.com. Updated November 24, 2020a. Accessed November 24, 2021.
- Rubini NPM, Ensina LFC, Silva EMK, Sano F, Sole D. Effectiveness and safety of omalizumab in the treatment of chronic spontaneous urticaria: Systematic review and meta-analysis. *Allergol Immunopathol (Madr)*. 2019;47(6):515-522. doi: 10.1016/j.aller.2019.05.003.
- Saini S. Chronic spontaneous urticaria: clinical manifestations, diagnosis, pathogenesis, and natural history. UpToDate Web site. https://www.uptodate.com. Updated January 25, 2021. Accessed November 19, 2021.
- Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Derm*. 2015;135:67-75.
- Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2019;94(10):1149-1167. doi: 10.1002/ajh.25617.
- Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254-61.
- Virchow JC, Katial R, Brusselle GG, et al. Safety of reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from 6 trials. *J Allergy Clin Immunol Pract*. 2020;8(2):540-548. doi: 10.1016/j.jaip.2019.07.038.
- Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma and Allergy. 2014;7:53-65.
- Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017;376(20):1921-1932.
- Wu Q, Zhang Y, Kong W, et al. Which is the best biologic for nasal polyps: dupilumab, omalizumab, or mepolizumab? A network meta-analysis [published online ahead of print, 2021 Oct 4]. *Int Arch Allergy Immunol*. 2021;1-10. doi:10.1159/000519228.
- Xolair [package insert], South San Francisco, CA: Genentech, Inc. and East Hanover, NJ: Novartis Pharmaceuticals; July 2021.
- Yancey SW, Ortega HG, Keene ON, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;139(4):1167-1175.
- Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma*. 2018:1-10. doi: 10.1080/02770903.2018.1520865.
- Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA/LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2018;73(7):1393-1414.doi: 10.1111/all.13397.

Publication Date: December 10, 2021

Optum

Prior Authorization Guideline

Guideline Name: Vuity (pilocarpine) 1.25% ophthalmic solution

1 . Indications

Drug Name: **Vuity (pilocarpine)**
Presbyopia of the eye Indicated for the treatment of presbyopia in adults.

2 . Criteria

Product Name: **Vuity**	
Approval Length	1 month
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of presbyopia **AND** **2** - Prescribed by or in consultation with an ophthalmologist or optometrist **AND** **3** – The recipient is unable to use corrective lenses (e.g., eyeglasses or contact lenses) confirmed by medical records (e.g., chart notes) **AND** **4** - Vuity will not be prescribed concurrently with any ophthalmic pilocarpine formulations	

Product Name: **Vuity**	
Approval Length	6 month(s)
Therapy Stage	Reauthorization
Approval Criteria **1** - Documentation of positive clinical response to therapy (e.g., improvement in near vision in low light conditions without loss of distance vision) **AND** **2** - Prescribed by or in consultation with an ophthalmologist or optometrist	

Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30,2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
VUITY	0	0	0	0

Therapeutic Class Overview
Ophthalmic Agents, Intraocular Pressure (IOP)-Modifying

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, with an estimated 6.9 million people with severe visual impairment or blindness due to glaucoma (*WHO 2019*). Open-angle glaucoma is the most common form in those of European or African descent; other forms include angle-closure, developmental, and secondary glaucoma (*Jacobs 2020a*). Patients with open-angle glaucoma do not typically have symptoms, and it is usually detected with a comprehensive eye exam. If left untreated, progression to visual field loss and blindness can occur. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia (*Ellis et al 2000, Gedde et al 2021, Girkin et al 2004, Lesk et al 2007*).
- Elevated IOP is the only major risk factor for glaucoma that is directly treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage (*Jacobs 2020b*). Treatment may be initiated in patients with an elevated IOP despite having no visual field loss or optic nerve damage. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression (*Jacobs 2020a*). In general, a target IOP that is 25 to 30% lower than baseline is reasonable (*Jacobs 2020b*). The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life.
- The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 20 to 30% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further vis0ual loss and optic nerve damage will be prevented (*Gedde et al 2021*).
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). Medical intervention or laser therapy is generally used as initial therapy prior to surgical treatment (*Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors (*Gedde et al 2021, Jacobs 2020b*). These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow.
- The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*). Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents (*Jacobs 2020b*).
- Presbyopia ("aging sight") is a common, non-refractive and irreversible error of the eye that affects visual acuity, occurring normally due to aging, and usually begins at ≥ 40 years of age. The average age of those first reporting symptoms is between 42 to 44 years of age. Presbyopia has most commonly been treated with use of lenses, including convex lenses ("reading glasses") or in combination with lens with correction for distance viewing (eg, bifocals, trifocals, etc.). In the United States (U.S.), presbyopia is the most common cause of visual impairment, with 76 million Americans born between 1946 and 1964 (*AAO 2021, Katz et al 2021, Mian 2021*).
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha-Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03%, which is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1%*	-
Alphagan P (brimonidine tartrate ophthalmic solution) 0.15%*	✔
brimonidine tartrate ophthalmic solution 0.2% ‡	✔
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	-
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
levobunolol hydrochloride ophthalmic solution 0.5% ††	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	✔
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%§§	✔
Vuity (pilocarpine ophthalmic solution) 1.25%	-
Prostaglandin Analogues¥	
bimatoprost ophthalmic solution 0.03% **	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% **	-
Travatan Z (travoprost ophthalmic solution) 0.004%	✔
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	- ‡‡
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	✔
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Rocklatan (latanoprost/netarsudil ophthalmic solution) 0.005%/0.02%	-
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is available as a branded product only.
‖ Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
¥ A bimatoprost 10 mcg ocular implant for intracameral administration (Durysta) was approved in March 2020 for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Due to its method of administration, this product is outside the scope of this review and will not be discussed further.

** Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
†† Brand Betagan is no longer available.
‡‡ A generic is approved by the Food and Drug Administration (FDA) but is not currently marketed.
§§ Brand Isopto Carpine 4% is no longer available.

(*Drugs@FDA 2022, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2022*)

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate)*	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol hydrochloride	✔ ‡			
Istalol (timolol maleate)	✔			
levobunolol hydrochloride	✔ ‡			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	✔			
Trusopt (dorzolamide)	✔			
Prostaglandin Analogues				
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Xalatan (latanoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Rhopressa (netarsudil)	✔			
Combinations				
Combigan (brimonidine/timolol) ‖				✔
Rocklatan (latanoprost/netarsudil)	✔			
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(*Prescribing information: Alphagan P 2013, apraclonidine 2022, Azopt 2021, betaxolol hydrochloride ophthalmic solution 2022, Betimol 2018, Betoptic S 2021, bimatoprost ophthalmic solution 0.03% 2020, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2012, Combigan 2015, Cosopt 2020, Cosopt PF 2017, levobunolol ophthalmic solution 2016, Iopidine 2021, Istalol 2019, Lumigan 2020, Rocklatan 2020, Rhopressa 2019, Simbrinza 2021, Timoptic 2020, Timoptic in Ocudose 2020, Timoptic-XE 2021, Travatan Z 2020, Trusopt 2020, Vyzulta 2019, Xalatan 2020, Xelpros 2021, Zioptan 2021*)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Presbyopia
Miotics					
Isopto Carpine (pilocarpine)	✔	✔	✔	✔	
Vuity (pilocarpine)					✔

(*Prescribing information: Isopto Carpine 2020, Vuity 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

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient-reported outcomes, or visual impairment. Very little direct comparative evidence is available (*Boland et al 2012, Boland et al 2013*).
- A network meta-analysis included 114 randomized controlled trials (N = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma (*Li et al 2016*). All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- Another network meta-analysis of 106 trials (N = 18,523) that compared single agents to each other or placebo and reported 3-month IOP outcomes did not find significant differences between latanoprostene bunod and latanoprost, tafluprost, or bimatoprost (both 0.01% and 0.03%). Bimatoprost 0.03% was ranked highest for likelihood of being the most effective, followed by latanoprostene bunod and then bimatoprost 0.01% (*Harasymowycz et al 2021*).
- A network meta-analysis evaluated 72 randomized controlled trials (N = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia except the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (N = 6841) and trough (N = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol (*Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008*). Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6-week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3-month study (*Coleman et al 2003*). However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open-angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy (*Barnes et al 1999, Chen et al 2001, Chen 2005, Sterk et al 1998*).
- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% ($p \leq 0.025$). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% ($p = 0.014$). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient ($p < 0.001$) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (N = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma (*Zhang et al 2017*). Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs apraclonidine (3 randomized controlled trials), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether 1 medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline (*Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989*).
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) (*Vogel et al 1989*).
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP (*Berry et al 1984, Stewart et al 1986*).
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant (*Berry et al 1984, Vogel et al 1989*).
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p

values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) (*Watson et al 2001*).

- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% (*Berson et al 1985, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998*).
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) (*Krieglstein et al 1987*).
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event ($p = 0.024$). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group ($p < 0.001$) (*Halper et al 2002*).
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) (*Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002*). The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% ($p < 0.05$) and also caused more stinging and burning ($p = 0.001$) (*Mundorf et al 2004*).
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing ($p = 0.04$ for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS ($p = 0.04$). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment ($p = 0.024$); however, this was not found to be significant at 24 weeks of treatment (*Shedden et al 2001*).

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect (*Cantor et al 2001, Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004*).
  - In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
  - Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*Haneda et al 2006, March et al 2000, Varma et al 2009*).
  - In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) (*Walters et al 2004*).
  - In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) (*Ikeda et al 2008*).

Carbonic Anhydrase Inhibitors

- Trials that support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2021, Trusopt prescribing information 2014*). However, the efficacy of ophthalmic carbonic anhydrase inhibitors appears to be inferior to other newer pharmacologic options for treating open-angle glaucoma (*Jacobs 2020b*).
- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel-group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) (*Silver 1998*). In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide

compared to dorzolamide (p < 0.001). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event (*Silver 2000*).
- Similar reductions in IOP were also observed when the agents were used in combination with timolol (*Michaud et al 2001*).

Carbonic Anhydrase Inhibitors compared to other classes
- The single agent carbonic anhydrase inhibitors were compared to beta-blockers (*March et al 2000, Rusk et al 1998, Strahlman et al 1995*). Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel-group, randomized controlled trial, timolol 0.5% was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily (p = 0.0002) (*March et al 2000*).
  - When dorzolamide 2% was compared to betaxolol 0.5% or timolol 0.5% in a 1 year, double-blind, parallel-group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) (*Strahlman et al 1995*).
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) (*Rusk et al 1998*).
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy (p < 0.001 for both groups) (*Bournias et al 2009*).

Miotics
- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics (eg, pilocarpine products) are very limited. These agents have been available for many years and are recognized as an established treatment option (*Jacobs 2021b*).
- The safety and efficacy of Vuity (pilocarpine) were evaluated in 2 multicenter, parallel-group, randomized controlled trials (GEMINI 1 and GEMINI 2), which included a total of 750 adults (n = 375 administered Vuity) aged 40 to 55 years diagnosed with presbyopia. The proportion of patients gaining ≥ 3 lines in high contrast, binocular distance corrected near visual acuity (DCNVA), without losing ≥ 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was significantly greater with pilocarpine vs vehicle (31% vs 8% in GEMINI 1; 26% vs 11% in GEMINI 2; p < 0.01 in each trial) at Day 30 (hour 3). A total of 6 (1.6%) patients and 4 (1.1%) patients treated with Vuity or vehicle, respectively, discontinued due to treatment-emergent adverse events (*Vuity prescribing information 2021, Waring et al 2021*).

Miotics compared to other drug classes
- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues (*Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999*). A trial evaluated pilocarpine plus a beta-blocker and found that pilocarpine was an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues (*Diestelhorst et al 2000*).
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery (*Ren et al 1999*).

Prostaglandin Analogues
- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost (*Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012, Tang et al 2019*).
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72),

and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk (*Lin et al 2014*).
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 PM (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point (*Aptel et al 2008*).
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patients with open-angle glaucoma or ocular hypertension (*Li et al 2006*).
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) (*Honrubia et al 2009*).
  - A meta-analysis (17 trials, N = 2433) comparing latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% found that bimatoprost 0.03% was associated with greater IOP reduction after 3 and 6 months of therapy compared to latanoprost 0.005% and after 3 months of therapy compared to travoprost 0.004%. Latanoprost 0.005% had the lowest rates of conjunctival hyperemia (*Tang et al 2019*).
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data have not been included in many meta-analyses. Available trials and meta-analyses suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost (*Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010b, Yang et al 2020*).
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) (*Traverso et al 2010*).
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups (*Schnober et al 2010*).
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments (*Uusitalo et al 2010b*).
  - A randomized trial compared IOP fluctuations among patients with newly diagnosed open-angle glaucoma who received latanoprost 0.005%, travoprost 0.004%, and tafluprost 0.0015%. Patients underwent IOP measurement at 8 AM, 2 PM, and 8 PM at baseline and weeks 2 and 6. At all time points, IOP reductions and fluctuations were similar between treatment groups. Tolerability was also similar between groups (*Faseeh et al 2021*).
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; p = 0.049) (*Uusitalo et al 2010a*).
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) (*Chabi et al 2012*).
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; n = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016, Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% (*Weinreb et al 2015*).

- Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
- A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in three Phase 3, randomized, double-masked, active control, parallel-group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points (*Rhopressa Prescribing Information 2019, Serle et al 2018*).
  - Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
  - In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Serle et al 2018*).
  - In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Serle et al 2018*).
  - In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg in the per-protocol population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 27 mmHg and < 30 mmHg in the per-protocol population (*Khouri et al 2019*).
  - Safety analyses have demonstrated that the drug is well-tolerated, with conjunctival hyperemia as the most frequent adverse event, and maintains consistently lowered IOP through 12 months of therapy (*Kahook et al 2019*).
- In a pooled analysis of data from the ROCKET-1 to 4 studies, efficacy of netarsudil 0.02% (n = 494) demonstrated non-inferiority to timolol 0.5% (n = 510) in patients with open-angle glaucoma or ocular hypertension with an IOP < 25 mmHg. The mean IOP through 3 months of treatment was 16.4 to 18.1 mmHg with netarsudil compared to 16.8 to 17.6 mmHg with timolol. Conjunctival hyperemia occurred more often with netarsudil (54.4%) compared to timolol (10.4%) (*Singh et al 2020*).
- Netarsudil was also evaluated in a 28-day, Phase 2, dose-response, double-masked, active control, parallel-group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline (*Craven et al 2005, Goñi et al 2005, Sherwood et al 2006*). In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study (*Katz et al 2012*). The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to

2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.

- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3-month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group (*Katz et al 2013, Nguyen et al 2013, Realini et al 2013*).
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months (*Whitson et al 2013*). Another trial evaluating twice daily dosing was conducted after the U.S. approval of the thrice daily dosing. Results were similar to those previously observed (*Aung et al 2014*).
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks (*Kozobolis et al 2017*).
- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment (*Clineschmidt et al 1998*).
  - One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation (*Renieri et al 2010*). Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.
- Rocklatan (netarsudil/latanoprost)
  - The efficacy and safety of the combination of netarsudil/latanoprost were established in 2 double-masked, multicenter, randomized controlled trials. In both, the fixed-dose combination was compared to its individual components, and patients were followed for 12 months and 3 months, respectively. Both trials found that netarsudil/latanoprost significantly lowered the mean IOP compared to either monotherapy (eg, netarsudil and latanoprost) at all time points through month 3. The IOP reductions were maintained for 12 months in the longer duration trial. Adverse events were mostly ocular in nature, and the combination group experienced higher rates of conjunctival hyperemia, eye pruritis, and cornea verticillata compared to each monotherapy group (*Asrani et al 2019, Asrani et al 2020, Rocklatan Prescribing Information 2020*).
- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) (*Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012*). However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; $p = 0.03$) (*Garcia-Feijoo et al 2010*). In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; $p < 0.001$). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol ($p = 0.03$ and $p = 0.012$, respectively) (*Konstas et al 2012*). It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Gedde et al 2021)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, are relatively safe, and are used once daily. They are often considered as initial medical therapy

unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)
- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open-angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

American Optometric Association (AOA) – Care of the Patient with Visual Impairment (*AOA 2007*)

The 2007 AOA guideline defines presbyopia as a reduction in accommodative ability that occurs normally with age and necessitates a plus lens addition for satisfactory seeing at near states. The AOA recommend that all visually impaired patients should undergo refraction to ensure optimal correction for best visual acuity and to determine the amount of magnification needed for certain tasks.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entities or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events. Beta-blockers may mask symptoms of hyperthyroidism such as tachycardia, and thyroid storm can occur with abrupt beta-blocker discontinuation.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

- Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including fundoscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
- Caution is advised when administering ophthalmic pilocarpine solution (Isopto Carpine) for control of IOP in pediatric patients with primary congenital glaucoma.
- Ophthalmic pilocarpine solution (Vuity) is not recommended when iritis is present because adhesions (synechiae) may form between the iris and lens. Contact lenses should be removed prior to drug instillation, and 10 minutes should be allowed to pass prior to reinserting contact lenses.

○ Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.

○ ROCK inhibitor

- Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

• Adverse reactions

○ Alpha-Agonists

- The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
- Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
- The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.

○ Beta-blockers

- Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).

○ Carbonic Anhydrase Inhibitors

- Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
- Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste that have been reported in up to 30% of patients.

○ Miotics

- Most adverse events reported with the miotics are associated with the eye. The most common adverse events reported with ophthalmic pilocarpine solutions were blurred vision, eye irritation, eye pain, accommodative change, and/or visual impairment with Isopto Carpine and headache and conjunctival hyperemia with Vuity.

○ Prostaglandin Analogues

- The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.

○ ROCK inhibitor

- The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
  - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

• Drug interactions

○ Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.

- Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy: Unclassified†
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
levobunolol hydrochloride	Ophthalmic solution	Ophthalmic	Once or twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	Ophthalmic suspension	Ophthalmic	Three times daily	A 3-month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy: Unclassified†
Trusopt (dorzolamide)	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active-control trial.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Miotics				
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30-minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Vuity (pilocarpine)	Ophthalmic solution	Ophthalmic	Once daily	Studies did not include patients aged ≥ 65 years; it is unknown if they respond differently from younger patients. Presbyopia does not occur in children. There are no adequate studies of Vuity in pregnant women. If > 1 topical ophthalmic products are being used, products should be administered ≥ 5 minutes apart.
Prostaglandin Analogues				
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xalatan (latanoprost)	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				16 years of age; contraindicated in pediatric patients < 2 years. Pregnancy: Unclassified†
Cosopt/Cosopt PF (dorzolamide /timolol)	Ophthalmic solution Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy: Unclassified†
Rocklatan (latanoprost/netarsudil)	Ophthalmic solution Contains benzalkonium chloride 0.02% as a preservative	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). A target IOP between 25 and 30% lower than baseline is reasonable (*Gedde et al 2021, Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*).
  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory (*Gedde et al 2021*). Combination therapy can be given as separate drops or in fixed-dose combinations, which include brimonidine/timolol, brimonidine/brinzolamide, dorzolamide/timolol, and latanoprost/netarsudil.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Gedde et al 2021, Jacobs 2020b*).
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues (*Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018, Tang et al 2019*).
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma (*Jacobs 2020b*).
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy that require additional IOP reduction. Ophthalmic pilocarpine, more specifically Isopto Carpine, is indicated for the control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension; Vuity is indicated for presbyopia, which is an additional treatment option to reading glasses.

REFERENCES

- Alphagan P [package insert], Irvine, CA: Allergan, Inc.; September 2013.
- American Academy of Ophthalmology (AAO). EyeWiki: Presbyopia. December 7, 2021. https://eyewiki.org/Presbyopia. Accessed January 30, 2022.
- American Optometric Association (AOA). Optometric Clinical Practice Guideline. Care of the patient with open angle glaucoma. 2010. https://www.aoa.org/practice/clinical-guidelines/clinical-practice-guidelines?sso=y. Accessed January 27, 2022.
- American Optometric Association (AOA). Optometric clinical practice guideline. Care of the patient with visual impairment (low vision rehabilitation). 2007. https://www.aoa.org/practice/clinical-guidelines/clinical-practice-guidelines?sso=y. Accessed January 31, 2022.
- Apraclonidine 0.5% solution/drops [package insert]. Lake Forest, IL: Akorn, Inc.; January 2022.
- Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandins analogs. A meta-analysis of randomized controlled trials. *J Glaucoma*. 2008;17(8):667-673.
- Asrani S, Robin AL, Serle JB, et al; MERCURY-1 Study Group. Netarsudil/latanoprost fixed-dose combination for elevated intraocular pressure: three-month data from a randomized phase 3 trial. *Am J Ophthalmol*. 2019;207:248-257. doi: 10.1016/j.ajo.2019.06.016.
- Asrani S, Bacharach J, Holland E, et al. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: pooled efficacy/safety analysis of phase 3 MERCURY-1 and -2. *Adv Ther*. 2020;37(4):1620-1631. doi:10.1007/s12325-020-01277-2.
- Aung T, Laganovska G, Hernandez-Paredes T, et al. Twice-daily brinzolamide/brimonidine fixed combination versus brinzolamide or brimonidine in open-angle glaucoma or ocular hypertension. *Ophthalmology*. 2014;121(12):2348-2355.
- Azopt [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; June 2021.
- Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD; AR-13324-CS202 Study Group. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. *Ophthalmology.* 2015;122(2):302-307.
- Barnes SD, Compagna JA, Dirks MS, et al. Control of intraocular pressure elevations after argon laser trabeculoplasty: comparison of brimonidine 0.2% to apraclonidine 1%. *Ophthalmology*. 1999;106:2033-2037.
- Bayer A, Weiler W, Oeverhus U, et al; for Xplore Observation group. Two-year follow-up of latanoprost 0.005% monotherapy after changing from previous glaucoma therapies. *J Ocul Pharmacol Ther.* 2004;20(6):470-478.
- Berry DP, Van Buskirk M, Shields BM. Betaxolol and timolol: a comparison of efficacy and side effects. *Arch Ophthalmol*. 1984;102:42-45.
- Berson FG, Cohen HB, Foerster RJ, et al. Levobunolol compared to timolol for the long-term control of elevated intraocular pressure. *Arch Ophthalmol*. 1985;103:379-382.

- Betaxolol hydrochloride ophthalmic solution [package insert], Lake Forest, IL: Akorn, Inc.; January 2022.
- Betimol [package insert], Lake Forest, IL: Akorn, Inc.; July 2018.
- Betoptic S [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; June 2021.
- Bimatoprost ophthalmic solution [package insert], Weston, FL: Apotex Corp.; November 2020.
- Boland MV, Ervin AM, Friedman D, et al. Treatment for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review No. 60. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061- I.) AHRQ Publication No. 12-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. https://effectivehealthcare.ahrq.gov/topics/glaucoma-treatment/research. Accessed January 27, 2022.
- Boland MV, Ervin AM, Friedman DS, et al. Comparative Effectiveness of Treatments for Open-Angle Glaucoma: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;158:271-279.
- Bournias TE, Lai J. Brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% compared as adjunctive therapy to prostaglandin analogs. *Ophthalmology.* 2009;116:1719-1724.
- Brimonidine tartrate ophthalmic solution [package insert], Tampa, FL: Bausch & Lomb Inc.; November 2018.
- Cantor LB, Hoop J, Katz JL, et al. Comparison of the clinical success and quality-of-life impact of brimonidine 0.2% and betaxolol 0.25% suspension in patients with elevated intraocular pressure. *Clin Ther*. 2001;23(7):1032-1039.
- Cantor LB, Liu CC, Batoosingh AL, et al. Safety and tolerability of brimonidine purite 0.1% and brimonidine purite 0.15%: a meta-analysis of two phase 3 studies. *Curr Med Res Opin*. 2009;25(7):1615-1620.
- Carteolol hydrochloride ophthalmic solution [package insert], Princeton, NJ: Sandoz Inc.; March 2012.
- Chabi A, Varma R, Tsai J, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*. 2012;153(6):1187-1196.
- Chen TC, Ang RT, Crosskreutz CL, et al. Brimonidine 0.2% vs. apraclonidine 0.5% for prevention of intraocular pressure elevations after anterior segment laser surgery. *Ophthalmology*. 2001;108:1033-1038.
- Chen TC. Brimonidine 0.15% vs. apraclonidine 0.5% for prevention of intraocular pressure elevation after anterior segment laser surgery [abstract]. *J Cataract Refract Surg*. 2005;31(9):1707-1712.
- Cheng J, Wei R. Meta-analysis of 13 randomized controlled trials comparing bimatoprost with latanoprost in patients with elevated intraocular pressure. *Clin Ther*. 2008;30(4):662-632.
- Cheng J, Xi G, Wei, R, et al. Efficacy and tolerability of latanoprost compared to dorzolamide combined with timolol in the treatment of patients with elevated intraocular pressure: a meta-analysis of randomized, controlled trials. *J Ocul Pharmacol Ther*. 2009:25(1);55-64.
- Clineschmidt C, Williams R, Snyder E, et al; Dorzolamide-Timolol Combination Study Group. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. *Ophthalmology.* 1998;105:1952-1959.
- Coleman AL, Lerner F, Bernstein P, et al; for the Lumigan/Cosopt Study Group. A three-month randomized controlled trial of bimatoprost (Lumigan®) vs. combined timolol and dorzolamide (Cosopt®) in patients with glaucoma or ocular hypertension. *Ophthalmology*. 2003;110(12):2362-2368.
- Combigan [package insert], Irvine, CA: Allergan Inc.; October 2015.
- Cosopt [package insert], Lake Forest, IL: Akorn, Inc.; December 2020.
- Cosopt PF [package insert], Lake Forest, IL: Akorn Pharmaceuticals.; June 2017.
- Craven ER, Walters TR, Williams R, et al; for the COMBIGAN study group. Brimonidine and timolol fixed-combination therapy versus monotherapy: a 3-month randomized trial in patients with glaucoma or ocular hypertension. *J Ocul Pharmacol Ther*. 2005;21(4):337-348.
- Diestelhorst M and the German Latanoprost Study group. The additive intraocular pressure-lowering effect of latanoprost 0.005% daily once and pilocarpine 2% t.i.d. in patients with open-angle glaucoma or ocular hypertension: a 6-month, randomized, multicenter study. *Graefe's Arch Clin Exp Ophthalmol.* 2000;238:433-439.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. 2021. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 27, 2022.
- Ellis JD, Evans JM, Ruta DA, et al. Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma? DARTS/MEMO collaboration. Diabetes Audit and Research in Tayside Study. Medicines Monitoring Unit. *Br J Ophthalmol*. 2000;84(11):1218-1224.
- Evans DW, Harris A, Cantor LB. Primary open-angle glaucoma patients characterized by ocular vasospasm demonstrate a different ocular vascular response to timolol versus betaxolol. *J Ocul Pharmacol Ther*. 1999:15(6):479-487.
- Faseeh AE, Allam RS, Shalash AB, Abd Elmohsen MN. Comparison between latanoprost, travoprost, and tafluprost in reducing intraocular pressure fluctuations in patients with glaucoma. *Eur J Ophthalmol*. 2021 Jan 26; 1120672121990540. doi:10.1177/1120672121990540.
- Fechtner RD, Airaksinen PJ, Getson AJ, et al. Efficacy and tolerability of dorzolamide 2%/timolol 0.5% combination (COSOPT™) vs. latanoprost 0.005% (Xalatan™) in the treatment of ocular hypertension of glaucoma: results from two randomized clinical trials. *Acta Ophthalmologica Scan*. 2004;82(1);42-48.
- Garcia-Feijoo J, Saenz-Frances F, Martinez-de-la-Casa JM, et al. Comparison of ocular hypotensive actions of fixed combinations of brimonidine/timolol and dorzolamide/timolol. *Curr Med Res Opin.* 2010;26(7):1599-1606.
- Gedde SJ, Vinod K, Wright MM, et al. American Academy of Ophthalmology (AAO): Primary Open-Angle Glaucoma Preferred Practice Pattern Guidelines. *Ophthalmology*. 2021;128(1):P71-P150. doi: 10.1016/j.ophtha.2020.10.022.
- Geyer O, Lazar M, Novack GD, et al. Levobunolol compared to timolol: a four-year study. *Br J Ophthalmol*. 1998;72:892-896.
- Girkin CA, McGwin G Jr, McNeal SF, et al. Hypothyroidism and the development of open-angle glaucoma in a male population. *Ophthalmology*. 2004;111(9):1649-1652.
- Goñi FJ; Brimonidine/Timolol Fixed Combination Study Group. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. *Eur J Ophthalmol*. 2005;15(5):581-590.
- Gulkilik G, Oba E, Odabasi M. Comparison of fixed combinations of dorzolamide/timolol and brimonidine/timolol in patients with primary open-angle glaucoma. *Int Ophthalmol.* 2011;31:447-451.
- Halper LK, Johnson-Pratt L, Dobbins T, et al. A comparison of the efficacy and tolerability of 0.5% timolol maleate ophthalmic gel-forming solution QD and 0.5% levobunolol hydrochloride BID in patients with ocular hypertension or open-angle glaucoma. *J Ocul Pharmacol Ther*. 2002;18(2):105-113.

- Haneda M, Shirato S, Maruyama K, et al. Comparison of the additive effects of nipradilol and carteolol to latanoprost in open-angle glaucoma. *Jpn J Ophthalmol*. 2006;50:33-37.
- Harasymowycz P, Royer C, Cui AX, et al. Short-term efficacy of latanoprostene bunod for the treatment of open-angle glaucoma and ocular hypertension: a systematic literature review and a network meta-analysis. *Br J Ophthalmol*. 2021 Jan 4;bjophthalmol-2020-317262. doi:10.1136/bjophthalmol-2020-317262.
- Hartenbaum D, Maloney S, Vaccarelli L, et al. Comparison of dorzolamide and pilocarpine as adjunctive therapy in patients with open-angle glaucoma and ocular hypertension. *Clin Ther.* 1999;21(9):1533-1538.
- Honrubia F, Garcia-Sanchez J, Polo V, et al. Conjunctival hyperemia with the use of latanoprost vs. other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomized clinical trials. *Br J Ophthalmol*. 2009;93(3);316-321.
- Ikeda Y, Mori K, Ishibashi T, et al. Effects of switching from topical B-blockers to latanoprost on intraocular pressure in patients with normal-tension glaucoma. *J Ocul Pharmacol Ther*. 2008;24(2):230-234.
- Iopidine [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; October 2021.
- Isopto Carpine [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
- Istalol [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; October 2019.
- Jacobs DS. Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis. UpToDate Web site. https://www.uptodate.com. Updated August 4, 2020a. Accessed January 27, 2022.
- Jacobs DS. Open-angle glaucoma: Treatment. UpToDate Web site. https://www.uptodate.com. Updated November 16, 2020b. Accessed January 27, 2022.
- Kahook MY, Serle JB, Mah FS, et al. Long-term safety and ocular hypotensive efficacy evaluation of netarsudil ophthalmic solution: rho kinase elevated IOP treatment trial (ROCKET-2). *Am J Ophthalmol*. 2019;200:130-137. doi: 10.1016/j.ajo.2019.01.003.
- Kammer JA, Katzman B, Ackerman SL, et al. Efficacy and tolerability of bimatoprost vs. travoprost in patients previously on latanoprost: a three-month, randomized, masked-evaluator, multicentre study. *Br J Ophthalmol*. 2010;94(1):74-79.
- Katz G, Dubiner H, Samples J, et al. Three-Month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724-730.
- Katz JA, Karpecki PM, Dorca A, et al. Presbyopia - a review of current treatment options and emerging therapies. *Clin Ophthalmol*. 2021;15:2167-2178.
- Katz LJ, Rauchman SH, Cottingham AJ, et al. Fixed-combination brimonidine-timolol versus latanoprost in glaucoma and ocular hypertension: a 12-week, randomized, comparison study. *Curr Med Res Opin*. 2012;28(5):781-788.
- Khouri AS, Serle JB, Bacharach J, et al. Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients with Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study. *Am J Ophthalmol*. 2019;204:97-104. doi: 10.1016/j.ajo.2019.03.002.
- Konstas AG, Quaranta L, Yan DB, et al. Twenty-four hour efficacy with the dorzolamide/timolol fixed-combination compared with the brimonidine/timolol fixed-combination in primary open-angle glaucoma. *Eye (London).* 2012;26(1):80-87.
- Konstas AGP, Kozobolis VP, Tsironi S, et al. Comparison of the 24-hour intraocular pressure-lowering effects of latanoprost and dorzolamide/timolol fixed combination after two and six months of treatment. *Ophthalmology*. 2008;115(1);99-103.
- Konstas AGP, Quaranta L, Katsanos A, et al. Twenty-four hour efficacy with preservative free tafluprost compared with latanoprost in patients with primary open angle glaucoma or ocular hypertension. *Br J Ophthalmol*. 2013;97(12):1510-1515.
- Kozobolis V, Panos GD, Konstantinidis A, Labiris G. Comparison of dorzolamide/timolol vs. brinzolamide/brimonidine fixed combination therapy in the management of primary open-angle glaucoma. *Eur J Ophthalmol*. 2017;27(2):160-163.
- Krieglstein GK, Novack GD, Voepel E, et al. Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol.* 1987;71:250-253.
- Lesk MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(11):1965-1972.
- Lesk MR, Koulis T, Sampalis F, et al. Effectiveness and safety of dorzolamide-timolol alone or combined with latanoprost in open-angle glaucoma or ocular hypertension. *Ann Pharmacother*. 2008;42:498-504.
- Levobunolol ophthalmic solution [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; August 2016.
- Li F, Huang W, Zhang X. Efficacy and safety of different regimens for primary open-angle glaucoma or ocular hypertension: a systematic review and network meta-analysis. *Acta Ophthalmol*. 2018;96:e277-e284.
- Li N, Chen X, Zhou Y, et al. Travoprost compared to other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol*. 2006;34:755-765.
- Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma: a systematic review and network meta-analysis. *Ophthalmology*. 2016;123(1):129-140.
- Lin L, Zhao YJ, Chew PT, et al. Comparative efficacy and tolerability of topical prostaglandin analogues for primary open-angle glaucoma and ocular hypertension. *Ann Pharmacother*. 2014;48(12):1585-1593.
- Lumigan [package insert], Allergan; Irvine, CA; September 2020.
- March W, Ochsner K; Brinzolamide Long-Term Therapy Study Group. The long-term safety and efficacy of brinzolamide 1.0% (Azopt®) in patients with primary open-angle glaucoma or ocular hypertension. *Am J of Ophthalmol.* 2000;129:136-143.
- Martinez A, Sanchez-Salorio M. Predictors for visual field progression and the effects of treatment with dorzolamide 2% or brinzolamide 1% each added to timolol 0.5% in primary open-angle glaucoma. *Acta Ophthalmol.* 2010;88:541-552.
- Medeiros FA, Martin KR, Peace J, et al. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.
- Mian SI. Visual impairment in adults: refractive disorders and presbyopia. UpToDate Web site. Updated September 15, 2021. www.uptodate.com. Accessed January 30, 2022.
- Michaud JE, Friren B; International Brinzolamide Adjunctive Study Group. Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Am J Ophthalmol.* 2001;132:235-243.
- Miki H, Miki K. The effects on the intraocular pressure and visual field resulting from a switch in the treatment from timolol to betaxolol. *J Ocul Pharmacol Ther*. 2004:20(6):509-517.

- Mundorf TK, Ogawa T, Naka H, et al. A 12-month, multicenter, randomized, double-masked, parallel-group comparison of timolol-LA once daily and timolol maleate ophthalmic solution twice daily in the treatment of adults with glaucoma or ocular hypertension. *Clin Ther*. 2004;26(4):541-551.
- Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther*. 2013;29(3):290-297.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. 2021. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 27, 2022.
- Ozturk F, Ermis SS, Inan UU. Comparison of the ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure: a six month study. *Acta Ophthalmol Scand*. 2007;85:80-83.
- Realini T, Nguyen QH, Katz G, et al. Fixed-combination brinzolamide 1%/brimonidine 0.2% vs. monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies. *Eye (Lond).* 2013;27(7):841-847.
- Ren J, Shin DH, Chung HS, et al. Efficacy of apraclonidine 1% versus pilocarpine 4% for prophylaxis of intraocular pressure spike after argon laser trabeculoplasty. *Ophthalmology*. 1999;106:1135-1139.
- Renieri G, Fuhrer K, Scheithe K, et al. Efficacy and tolerability of preservative-free eye drops containing a fixed combination of dorzolamide and timolol in glaucoma patients. *J Ocul Pharmacol Ther.* 2010;26(6):597-603.
- Rhopressa [package insert], Irvine, CA: Aerie Pharmaceuticals, Inc.; March 2019.
- Rocklatan [package insert], Irvine, CA: Aerie Pharmaceuticals, Inc.; June 2020.
- Rusk C, Sharpe E, Laurence J, et al; Dorzolamide Comparison Study Group. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. *Clin Ther.* 1998;20(3):454-466.
- Sawada A, Yamamoto T, Takatsuka N. Randomized crossover study of latanoprost and travoprost in eyes with open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(1):123-129.
- Schenker HI, Silver LH, the Timolol gel-forming solution study group. Long-term intraocular pressure-lowering efficacy and safety of timolol maleate gel-forming solution 0.5% compared to Timoptic-XE 0.5% in a 12-month study. *Am J Ophthalmol*. 2000;130:145-150.
- Schnober D, Hofmann G, Maier H, et al. Diurnal IOP-lowering efficacy and safety of travoprost 0.004% compared to tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2010;4:1459-1463.
- Serle JB, Katz LJ, McLaurin E, et al; ROCKET-1 and ROCKET-2 Study Groups. Two Phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: rho kinase elevated IOP treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol*. 2018;186:116-127.
- Sharpe ED, Williams RD, Stewart JA, et al. A comparison of dorzolamide/timolol-fixed combination vs. bimatoprost in patients with open-angle glaucoma who are poorly controlled on latanoprost. *J Ocul Pharmacol Ther*. 2008;24(2):408-413.
- Shedden A, Laurence J, Tipping R, Timoptic-XE 0.5% study group. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution vs. timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study. *Clin Ther*. 2001;23(3):440-450.
- Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs. monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol*. 2006;124(9):1230-1238.
- Siesky B, Harris A, Ehrlich R, et al. Short-term effects of brimonidine/timolol and dorzolamide/timolol on ocular perfusion pressure and blood flow in glaucoma. *Adv Ther.* 2012;29(1):53-63.
- Singh IP, Fechtner RD, Myers JS, et al. Pooled efficacy and safety profile of netarsudil ophthalmic solution 0.02% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma.* 2020;29(10):878-884. doi: 10.1097/IJG.0000000000001634.
- Silver L, Brinzolamide Comfort Study Group. Ocular comfort of brinzolamide 1% ophthalmic suspension compared to dorzolamide 2% ophthalmic solution: results from two multicenter comfort studies. *Surv Ophthalmol.* 2000;44[suppl 2]:S141-145.
- Silver L, Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt®), a new tropical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol.* 1998;126:400-408.
- Simbrinza [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; May 2021.
- Sonty S, Mundorf TK, Stewart JA, et al. Short-term tolerability of once-daily timolol hemihydrate 0.5%, timolol maleate in sorbate 0.5%, and generic timolol maleate gel-forming solution 0.5% in glaucoma and/or ocular hypertension: a prospective, randomized, double-masked, active controlled, three-period, crossover pilot study. *Clin Ther*. 2009;31(10):2063-2071.
- Sterk CC, Bubberman-Renzenbrink AC, van Best JA. The effect of 1% apraclonidine on intraocular pressure after cataract surgery. *Ophthalmic Surg Lasers*. 1998;29(6):472-475.
- Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs. timolol: a six-month double-blind comparison. *Arch Ophthalmol*. 1986;104:46-48.
- Stewart WC, Sharpe ED, Stewart JA, et al. The safety and efficacy of timolol 0.5% in xanthan gum vs. timolol gel forming solution 0.5%. *Curr Eye Res*. 2002;24(5):387-391.
- Strahlman E, Tipping R, Vogel R; International Dorzolamide Study Group. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt®), timolol, and betaxolol. *Arch Ophthalmol.* 1995;113:1009-1016.
- Tang W, Zhang F, Liu K, Duan X. Efficacy and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. *Medicine (Baltimore)*. 2019;98(30):e16597. doi: 10.1097/MD.0000000000016597.
- Timoptic [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; February 2020.
- Timoptic in Ocudose [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; November 2020.
- Timoptic-XE [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; February 2021.
- Travatan Z [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
- Traverso CE, Ropo A, Papadia M, et al. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of tafluprost compared to latanoprost. *J Ocul Pharmacol Ther*. 2010;26(1):97-104.
- Trusopt [package insert], Whitehouse Station, NJ: Merck and Co., Inc.; December 2020.
- Uusitalo H, Chen E, Pfeiffer N, et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. *Acta Ophthalmol*. 2010a;88(3):329-336.

- Uusitalo H, Pillunat LE, Ropo A; Phase III Study Investigators. Efficacy and safety of tafluprost 0.0015% vs. latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. *Acta Ophthalmol*. 2010b;88(1):12-19.
- van der Valk R, Webers CAB, Lumley T, et al. A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. *J Clin Epidemiology*. 2009;62:1279-1283.
- Varma R, Hwang LJ, Grunden JW, et al. Assessing the efficacy of latanoprost vs. timolol using an alternate efficacy parameter: the intervisit intraocular pressure range. *Am J Ophthalmol*. 2009;148:221-226.
- Vogel R, Tipping R, Kulaga SF, et al; Timolol-Betaxolol Study Group. Changing therapy from timolol to betaxolol: effect on intraocular pressure in selected patients with glaucoma. *Arch Ophthalmol*. 1989;107:1303-1307.
- Vuity [package insert], North Chicago, IL: Allergan, an AbbVie company; October 2021.
- Vyzulta [package insert], Tampa, FL: Bausch & Lomb Inc.; May 2019.
- Walters TR, DuBiner HB, Carpenter SP, et al. 24-hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. *Surv Ophthalmol*. 2004;49(S1):S26-S35.
- Walters TR, Maloney S, Slater D, et al. Efficacy and tolerability of 0.5% timolol maleate ophthalmic gel-forming solution QD compared to 0.5% levobunolol hydrochloride BID in patients with open-angle glaucoma or ocular hypertension. *Clin Ther*. 1998;20(6):1170-1178.
- Waring GO, McCabe C, Wirta D, et al. GEMINI 1 & 2 pooled phase 3 safety and efficacy: AGN-190584 primary and key secondary endpoints [abstract]. Presented at: AAO; 2021 Nov 12 to 15; New Orleans, LA.
- Watson PG, Barnett MF, Parker V, et al. A seven-year prospective comparative study of 3 topical β blockers in the management of primary open angle glaucoma. *Br J Ophthalmol*. 2001;85:962-968.
- Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. Latanoprostene bunod 0.024% in subjects with open-angle glaucoma or ocular hypertension: pooled phase 3 study findings. *J Glaucoma*. 2018;27(1):7-15.
- Weinreb RN, Ong T, Scassellati Sforzolini B, et al; VOYAGER study group. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99(6):738-745.
- Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
- Whitson JT, Realini T, Nguyen QH, et al. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol*. 2013;7:1053-1060.
- World Health Organization. World report on Vision. October 2019. https://www.who.int/publications/i/item/world-report-on-vision. Accessed January 27, 2022.
- Xalatan [package insert], Pfizer; New York, NY; September 2020.
- Xelpros [package insert], Sun Pharmaceutical Industries, Ltd; Cranbury, NJ; April 2021.
- Yang XT, Zhao L, Wang LJ, Zhang Y, Liao DY, Wang JM. Efficacy and safety of 0.0015% tafluprost versus 0.005% latanoprost in primary open angle glaucoma, ocular hypertension: a meta-analysis. *Int J Ophthalmol*. 2020;13(3):474-480. doi:10.18240/ijo.2020.03.16.
- Zhang L, Weizer JS, Musch DC. Perioperative medications for preventing temporarily increased intraocular pressure after laser trabeculoplasty. *Cochrane Database Syst Rev*. 2017;2:CD010746. doi: 10.1002/14651858.CD010746.pub2.
- Zhang WY, Wan Po AL, Dua HS, et al. Meta-analysis of randomized controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or hypertension. *Br J Ophthalmol*. 2001;85:983-990.
- Zioptan [package insert], Whitehouse Station, NJ: Merck and Co., Inc.; November 2021.

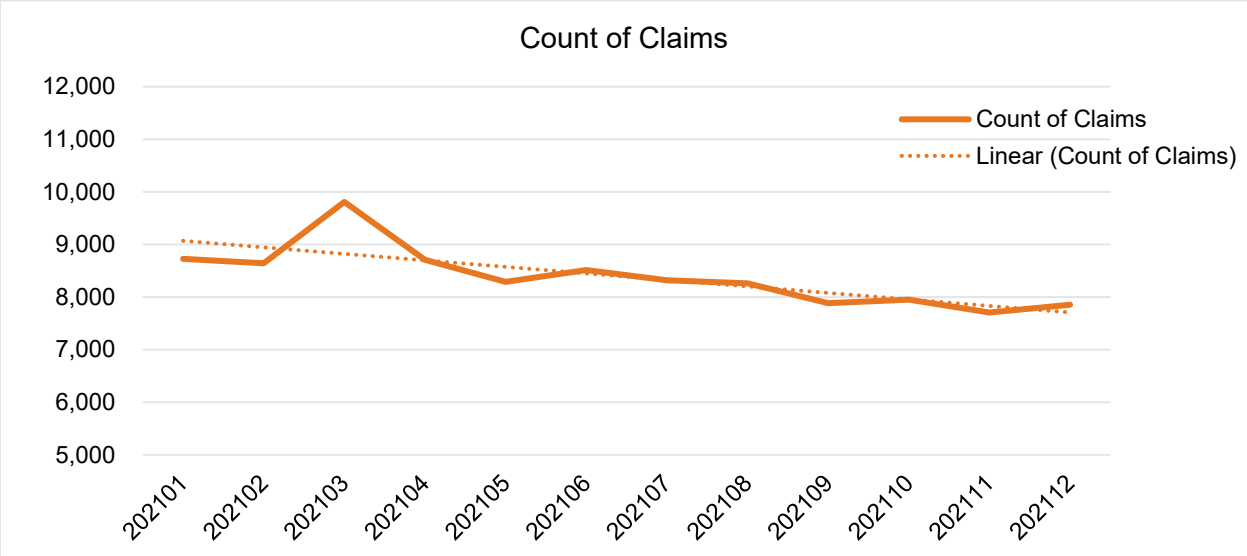
Publication Date: February 3, 2022

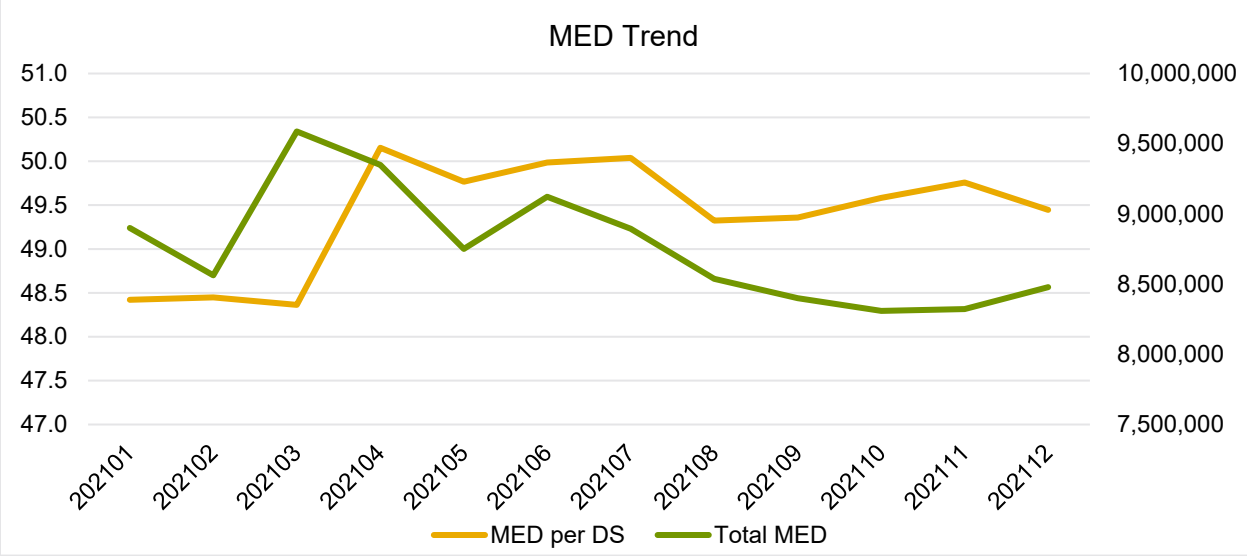
Board Requested Reports

Nevada Medicaid

Opioid Trends
Fee for Service
January 1, 2021 – December 31,2021

Date Filled	Count of Claims	Days Supply	Count of Members	Total Qty	Total MED	MED per DS
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
202104	8,708	186,404	7,708	630,228	9,348,850	50.2
202105	8,289	175,838	7,437	593,115	8,750,997	49.8
202106	8,513	182,492	7,505	619,603	9,122,032	50.0
202107	8,319	177,747	7,304	602,263	8,894,309	50.0
202108	8,263	173,105	7,259	585,982	8,538,198	49.3
202109	7,885	170,190	7,023	574,890	8,400,255	49.4
202110	7,952	167,582	7,070	572,780	8,309,278	49.6
202111	7,707	167,247	6,855	566,492	8,321,947	49.8
202112	7,853	171,476	6,893	578,938	8,478,756	49.4





Nevada Medicaid

Opioid Trends

Fee for Service

January 1, 2021 – December 31,2021

Member ID Encrypted	Diagnosis	Claim Count	Days Supply	Quantity	Total MED	MED per DS
70C77D1191001	Vertebrogenic low back pain	3	90	390	37,800	990
75CA731794002	Obstruction of bile duct; Chronic pancreatitis	8	102	1,120	45,450	841
70CD7C1B94003	Chronic Pain Syndrome	6	180	1,080	57,600	640
7CC6761590004	Systemic lupus erythematosus	8	226	960	69,600	618
75CF741397005	Cervicalgia (Neck Pain)	6	168	924	45,360	540
77CF7C1090006	Cervical disc disorder with myelopathy	7	210	1350	48,150	525
75CF741397007	Intervertebral disc degeneration, lumbar region	8	240	840	57,600	480
72CA761496008	Chronic pain- low back and neck	5	150	510	37,800	480
74CF741594009	Vertebrogenic low back pain	14	339	912	34,870	434
7CCE701691010	Chronic Pain; Polyarthritis	6	180	720	36,450	405

Member ID Encrypted	Drug Label Name	Count of Claims	Days Supply	Total Quantity
70C77D1191001		3	90	390
	FENTANYL	1	30	30
	OXYCODONE HYDROCHLORIDE	2	360	360
75CA731794002		8	102	1,120
	OXYCODONE HYDROCHLORIDE	8	102	1,120
70CD7C1B94003		6	180	1,080
	MORPHINE SULFATE ER	3	90	540
	OXYCODONE HYDROCHLORIDE	3	90	540
7CC6761590004		8	226	960
	MORPHINE SULFATE ER	4	112	480
	OXYCODONE HYDROCHLORIDE	4	114	480
75CF741397005		6	168	924
	MORPHINE SULFATE ER	3	84	252
	OXYCODONE HYDROCHLORIDE	3	84	672
77CF7C1090006		7	210	1,350
	HYDROCODONE /ACETAMINOPHEN	4	120	360
	OXYCODONE HYDROCHLORIDE	3	90	990
75CF741397007		8	240	840
	MORPHINE SULFATE ER	4	120	360
	OXYCODONE HYDROCHLORIDE	4	120	480
72CA761496008		5	150	510
	MORPHINE SULFATE ER	3	90	270
	OXYCODONE HYDROCHLORIDE	2	60	240
74CF741594009		14	339	912
	OXYCODONE HYDROCHLORIDE	7	168	570
	XTAMPZA ER	7	171	342
7CCE701691010		6	180	720
	MORPHINE SULFATE ER	3	90	270
	OXYCODONE HYDROCHLORIDE	3	90	450

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
2021 Q4	Pres 1	LAS VEGAS	NV	-	179	405	11,378	40,211	692,684	61	0.34
2021 Q4	Pres 36	LAS VEGAS	NV	FAMILY NURSE PRACTITIONER	145	293	8,064	26,237	666,604	83	0.57
2021 Q4	Pres 9	LAS VEGAS	NV	PHYSICIAN ASSIST	136	318	9,244	31,546	597,383	65	0.48
2021 Q4	Pres 25	LAS VEGAS	NV	-	175	394	11,342	38,377	506,265	45	0.26
2021 Q4	Pres 14	RENO	NV	ANESTHESIOLOGY	72	182	5,362	16,536	422,397	79	1.09
2021 Q4	Pres 16	LAS VEGAS	NV	PHYSICIAN ASSIST	96	193	5,754	26,471	375,408	65	0.68
2021 Q4	Pres 3	LAS VEGAS	NV	ORTHOPEDIC SURGERY	109	251	6,919	25,558	375,337	54	0.50
2021 Q4	Pres 17	LAS VEGAS	NV	PHYSICIAN ASSIST	113	222	6,215	21,011	349,682	56	0.50
2021 Q4	Pres 19	LAS VEGAS	NV	FAMILY NURSE PRACTITIONER	118	291	8,588	27,131	348,645	41	0.34
2021 Q4	Pres 2	LAS VEGAS	NV	FAMILY NURSE PRACTITIONER	88	157	4,661	16,468	332,505	71	0.81
2021 Q3	Pres 1	LAS VEGAS	NV	FAMILY NURSE PRACTITIONER	170	321	9,008	28,848	718,938	80	0.47
2021 Q3	Pres 36	LAS VEGAS	NV	PHYSICIAN ASSIST	142	324	9,231	31,835	614,700	67	0.47
2021 Q3	Pres 9	LAS VEGAS	NV	-	158	350	9,716	34,144	601,250	62	0.39
2021 Q3	Pres 25	LAS VEGAS	NV	-	161	376	10,918	36,716	492,415	45	0.28
2021 Q3	Pres 14	SPARKS	NV	ANESTHESIOLOGY	126	272	7,912	31,412	464,850	59	0.47
2021 Q3	Pres 16	RENO	NV	ANESTHESIOLOGY	81	189	5,546	17,694	431,321	78	0.96
2021 Q3	Pres 3	LAS VEGAS	NV	ORTHOPEDIC SURGERY	126	259	7,170	25,995	401,280	56	0.44
2021 Q3	Pres 17	LAS VEGAS	NV	PHYSICIAN ASSIST	117	201	5,974	25,100	371,993	62	0.53
2021 Q3	Pres 19	LAS VEGAS	NV	-	102	210	6,258	21,500	354,703	57	0.56
2021 Q3	Pres 2	LAS VEGAS	NV	INTERNAL MEDICINE	49	131	3,841	15,183	332,130	86	1.76

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
2021 Q4	Pres 27	RENO	NV	INTERNAL MEDICINE	1	1	7	60	1,800	257	257
2021 Q4	Pres 18	LAS VEGAS	NV	ONCOLOGY	1	1	20	120	3,600	180	180
2021 Q4	Pres 20	LAS VEGAS	NV	FAMILY PRACTICE	1	3	90	360	16,200	180	180
2021 Q4	Pres 31	COTTONWOOD	AZ	Student- Organized Health Program	1	1	3	16	480	160	160
2021 Q4	Pres 37	LAS VEGAS	NV	INTERNAL MEDICINE	2	4	120	740	33,300	278	139
2021 Q4	Pres 34	PUYALLUP	WA	Student- Organized Health Program	1	1	30	90	4,050	135	135
2021 Q4	Pres 33	ORANGE	CA	PEDIATRICS-ONCOLOGY	1	1	14	56	1,680	120	120
2021 Q4	Pres 38	LAS VEGAS	NV	FAMILY NURSE PRACTITIONER	1	1	14	56	1,680	120	120
2021 Q4	Pres 12	RENO	NV	HEMATOLOGY/ONCOL, PEDS	1	1	30	150	3,375	113	113
2021 Q4	Pres 22	HENDERSON	NV	INTERNAL MEDICINE	2	6	180	1,080	40,500	225	113
2021 Q3	Pres 18	ELKO	NV	PEDIATRICS	1	5	72	25	18,000	250	250
2021 Q3	Pres 38	LAS VEGAS	NV	-	2	3	45	250	18,000	400	200
2021 Q3	Pres 39	SPARKS	NV	FAMILY PRACTICE	1	1	30	60	6,000	200	200
2021 Q3	Pres 5	LAS VEGAS	NV	FAMILY PRACTICE	1	4	105	420	18,900	180	180
2021 Q3	Pres 13	WEST JORDAN	UT	HEMATOLOGY/ONCOL, PEDS	1	3	90	30	16,200	180	180
2021 Q3	Pres 12	LAS VEGAS	NV	ONCOLOGY	1	3	60	360	10,800	180	180
2021 Q3	Pres 4	LAS VEGAS	NV	INTERNAL MEDICINE	1	1	29	114	5,130	177	177
2021 Q3	Pres 33	LAS VEGAS	NV	HEMATOLOGY/ONCOL, PEDS	1	1	30	90	4,050	135	135
2021 Q3	Pres 6	HOUSTON	TX	HEMATOLOGY	1	1	30	180	4,050	135	135
2021 Q3	Pres 8	DAYTON	OH	INTERNAL MEDICINE	1	1	7	42	945	135	135

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes Fee for Service

June 1, 2021 - December 31, 2021

Top 10 Classes by Claim Count

2021 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.**	26,598	$2,953,661.00
SYMPATHOMIMETICS**	19,618	$3,078,213.93
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	16,540	$208,249.20
OPIOID COMBINATIONS**	13,470	$419,130.12
CENTRAL MUSCLE RELAXANTS**	12,289	$199,689.16
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	12,179	$228,318.05
VIRAL VACCINES**	11,938	$489,403.31
HMG COA REDUCTASE INHIBITORS**	11,217	$153,946.47
ANTIANXIETY AGENTS - MISC.**	10,195	$150,409.65
DIBENZAPINES**	10,116	$339,019.78

2021 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.**	26,817	$2,955,666.57
SYMPATHOMIMETICS**	19,757	$3,141,924.68
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	16,613	$212,735.19
OPIOID COMBINATIONS**	14,022	$433,237.16
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)**	12,444	$265,460.52
CENTRAL MUSCLE RELAXANTS**	12,412	$202,425.05
VIRAL VACCINES**	12,052	$506,153.69
HMG COA REDUCTASE INHIBITORS**	11,637	$163,903.73
ANTIANXIETY AGENTS - MISC.**	10,247	$150,463.60
DIBENZAPINES**	10,146	$342,655.85

Top 10 Classes by Amount Paid

2021 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS**	130	$13,128,589.90
ANTIRETROVIRALS**	1,848	$4,127,882.98
INSULIN**	4789	$3,099,885.90
SYMPATHOMIMETICS**	19,618	$3,078,213.93
ANTIPSYCHOTICS - MISC.**	3,304	$3,014,017.60
ANTICONVULSANTS - MISC.**	26,598	$2,953,661.00
BENZISOXAZOLES**	5,947	$2,848,537.34
LOCAL ANESTHETICS - TOPICAL**	2,617	$2,639,260.35
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES**	319	$2,410,550.77
CYSTIC FIBROSIS AGENTS**	236	$2,400,357.66

2021 Q3

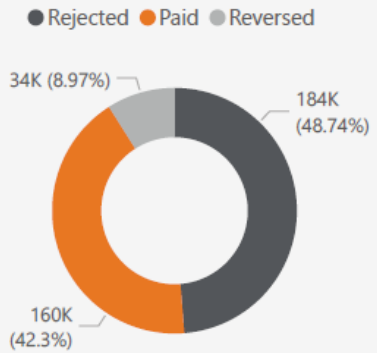
Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS**	128	$12,349,132.54
ANTIRETROVIRALS**	1,821	$4,201,292.88
INSULIN**	4,908	$3,211,271.30
SYMPATHOMIMETICS**	19,757	$3,141,924.68
ANTIPSYCHOTICS - MISC.**	3,329	$3,094,317.15
ANTICONVULSANTS - MISC.**	26,817	$2,955,666.57
BENZISOXAZOLES**	5,847	$2,742,851.62
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES**	313	$2,318,545.26
INCRETIN MIMETIC AGENTS (GLP-1 RECEPTOR AGONISTS)*	1,441	$2,185,203.09
CYSTIC FIBROSIS AGENTS**	211	$2,029,161.16

cDUR Quarterly Report

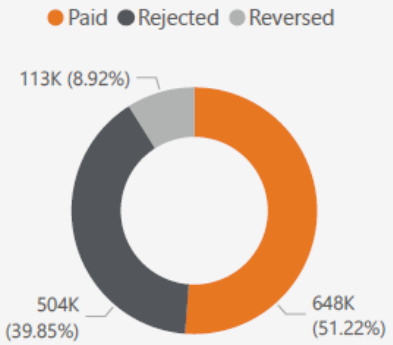
Start Date	End Date
Oct,2021	Dec,2021

Claims Summary

Interventions By Claim Status



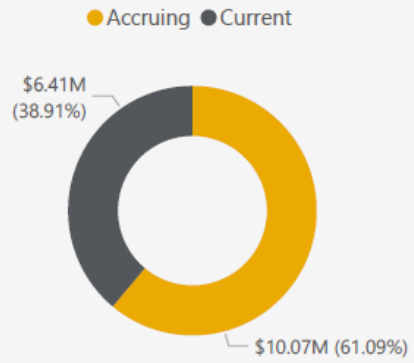
Total Rx By Claim Status



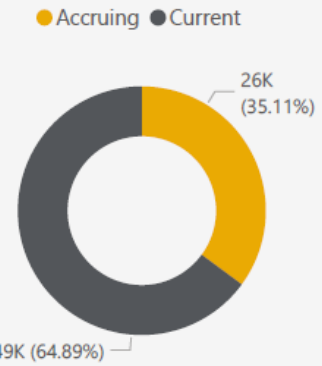
Claim Status	Total Rx	Interventions	% Total Rxs with Intervention
Rejected	503,848	183,968	36.51%
Reversed	112,814	33,841	30.00%
Paid	647,552	159,658	24.66%
Total	**1,264,214**	**377,467**	**29.86%**

Savings Outcome Analysis Summary

Savings



Successes

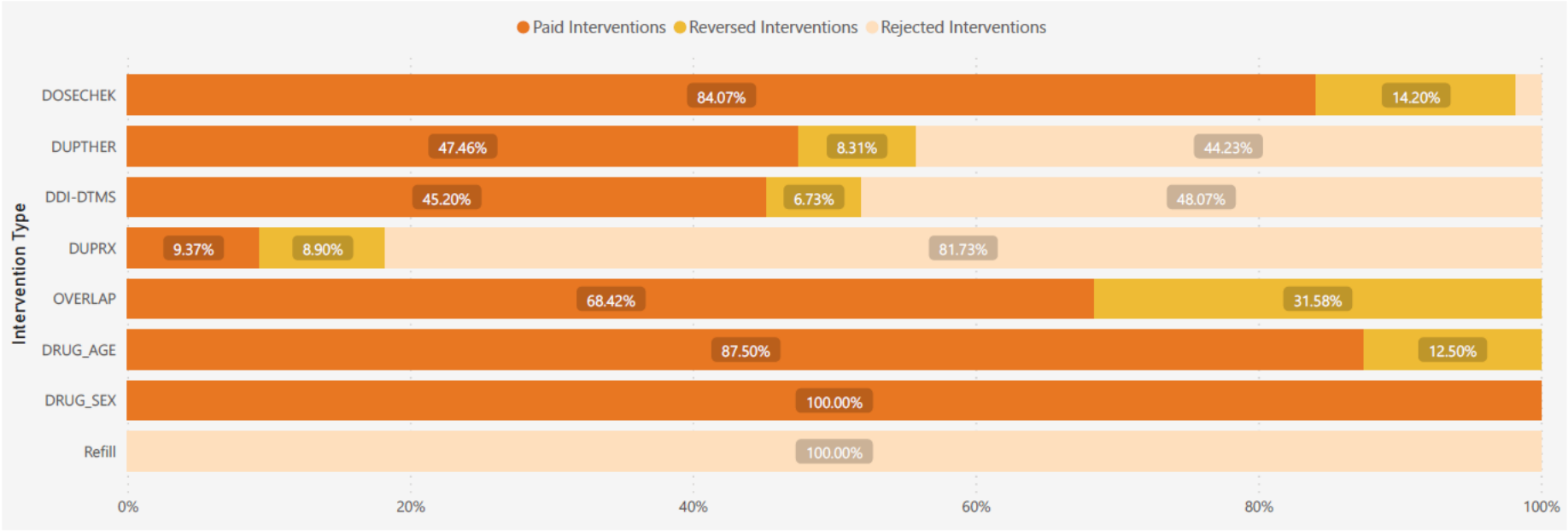


Type	Current	Accruing	Total	YTD
Savings	$6,411,233.10	$10,067,624.33	$16,478,857.43	$62,882,773.62
Success	48,729	26,370	75,099	191,916

cDUR Detailed Activity Summary : Tabular View

Intervention Type	Total	Paid Rx	Paid Rx%	Rejected Rx	Rejected %	Reversed Rx	Reversed %
Dosing/Duration (DOSECHEK)	61,298	51,531	84.1%	1,063	1.7%	8,704	14.2%
Duplicate Therapy (DUPTHER)	104,171	49,435	47.5%	46,075	44.2%	8,661	8.3%
Drug-Drug Interaction (DDI-DTMS)	108,462	49,023	45.2%	52,139	48.1%	7,300	6.7%
Duplicate Rx (DUPRX)	102,998	9,647	9.4%	84,182	81.7%	9,169	8.9%
Multiple Drug Screening (OVERLAP)	19	13	68.4%			6	31.6%
Drug Age Caution (DRUG_AGE)	8	7	87.5%			1	12.5%
Drug Sex Caution (DRUG_SEX)	2	2	100.0%				
Refill Too Soon	509			509	100.0%		
Total	**377,467**	**159,658**	**42.3%**	**183,968**	**48.7%**	**33,841**	**9.0%**

cDUR Detailed Activity Summary : Graphical View



cDUR Detailed Savings Outcome : Tabular View

Intervention Type	Current Success	Current Savings	Accruing Success	Accruing Savings	Total Success	Total Savings	YTD Success	YTD Savings
Duplicate Rx (DUPRX)	37,917	$3,331,087.11	9,815	$1,741,073.08	47,732	$5,072,160.19	149,653	$21,193,396.97
Duplicate Therapy (DUPTHER)	5,035	$1,303,317.75	10,221	$3,830,394.83	15,256	$5,133,712.58	20,232	$17,918,205.72
Drug-Drug Interaction (DDI-DTMS)	3,739	$260,180.28	4,216	$795,416.86	7,955	$1,055,597.14	14,832	$4,572,114.06
Dosing/Duration (DOSECHEK)	1,609	$1,474,223.68	2,067	$3,697,108.02	3,676	$5,171,331.69	5,611	$19,037,588.48
Refill Too Soon	429	$42,424.28	49	$3,566.96	478	$45,991.24	1,580	$158,747.09
Drug Age Caution (DRUG_AGE)	0	$0.00			0	$0.00	6	$211.15
Drug Sex Caution (DRUG_SEX)	0	$0.00	2	$64.59	2	$64.59	1	$2,474.43
Multiple Drug Screening (OVERLAP)	0	$0.00			0	$0.00	1	$35.71
Total	**48,729**	**$6,411,233.10**	**26,370**	**$10,067,624.33**	**75,099**	**$16,478,857.43**	**191,916**	**$62,882,773.62**

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 2021

Q4 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Opioid, Antipsychotic, and Benzodiazepine Utilization	235	11	126	235	4.7%