



Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 5th, 2026 1:00 - 5:00 PM

Remote Meeting via Zoom Platform

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333.

I. CALL TO ORDER

- | | | |
|---------|---|-----------------|
| 1:00 PM | A. Roll Call & Introductions | R. Citron (OSU) |
| | B. Conflict of Interest Declaration | R. Citron (OSU) |
| | C. Election of Chair and Vice-chair | R. Citron (OSU) |
| | D. Approval of Agenda and Minutes | R. Citron (OSU) |
| | E. Department Update | A. Gibler (OHA) |
| | F. Legislative Update | D. Weston (OHA) |
| | G. Mental Health Clinical Advisory Group Update | A. Gibler (OHA) |

1:20 PM II. CONSENT AGENDA TOPICS (Chair)

- A. Oncology Prior Authorization Updates
- B. Orphan Drug Policy Updates
 - 1. Public Comment

1:25 PM III. DUR ACTIVITIES

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|--|----------------------------|
| A. Quarterly Utilization Report | R. Citron (OSU) |
| B. ProDUR Report | L. Starkweather (Gainwell) |
| C. RetroDUR Report | D. Engen (OSU) |
| D. Oregon State Drug Review | K. Sentena (OSU) |
| 1. New Therapies for Treatment of Chronic Obstructive Pulmonary Disease | |
| 2. New Drugs for the Treatment of Uncomplicated Urinary Tract Infections | |
| 3. 2025 American College of Cardiology/American Heart Association Joint Committee Clinical Practice Guideline Update | |

IV. NEW BUSINESS

1:45 PM	A. Antidepressant Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:00 PM	B. Tryngolza® (Olezarsen) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations	M. Herink (OSU)
2:15 PM	C. Wegovy® (semaglutide) Prior Authorization for MASH 1. Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
2:30 PM	BREAK	
2:45 PM	D. Sedatives for Insomnia Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:00 PM	E. Medications for Allergies 1. Nasal Inhalers, Oral 1 st and 2 nd Generation antihistamines Class Update 2. Eye Drops for Allergies Class Review 3. Prior Authorization Criteria 4. Public Comment 5. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:30 PM	F. Forzinity™ (elamipretide) Abbreviated New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
3:50 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	



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OHA Health Policy & Analytics
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Jeanne Savage, MD	Physician	Medical Director, Trillium	Portland	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2028
Jennifer Henderson, DO	Physician	Asante Medical Director	Medford	December 2028
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2028

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Drug Use Research & Management Program

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, December 4th, 2025

1:05 PM - 4:45 PM

Via Zoom webinar

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence, and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee, and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD; Eriko Onishi, MD;

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Trevor Douglass, DC; Lan Starkweather, PharmD; Brandon Wells; Jennifer Bowen; Michael Yu, DC; Kyle Hamilton

Audience: Leland Turner*, Chiesi; Keith Liully*, Abeona; Andrea Hawkinson*, Recordati; Janelle Raymond*, IntraBio; Amber Svardal*, Precigen; Andrew Albanese, OHSU; Krystal Ngo*, Arcutis Biotherapeutics; Valerie Ng*, LEO Pharma; Joe Cirrincione*, Incyte; Shawn Akey, Concis Labs; Ron Abraham; Erin Estock, Arcutis; Gary Parenteau, Dexcom; Miranda Tyzenman, Artia Soln; Oyinda; Rosalie Elliott, Umpqua; William White, Abeona; Michael Foster, Ultragenyx; Lee Stout, Chiesi; Erin Nowak, AbbVie; Jessica Garrison, Gainwell Tech; Tammi Ocumpaugh, Otsuka; Chris Ferrin, IHN; Michele Pannell, Alkermes; Lisa Pulver; Brett Freund; Vivian Ton, UHA; Georgette Dzwilewski; Gloria Zepeda, AllCare; Lewis Backus, OHA; Daria Meleshkina, EOCCO; Jill Carol, BMS; Mark Kantor, AllCare; Courtney Ho; Trung Nguyen; Kim Michelet; Beth Giblin

(*) Provided verbal testimony

I. CALL TO ORDER

- A. Roll Call & Introductions
 - Meeting called to order at approx. 1:05 p.m., introductions by Committee and Staff
- B. Conflict of Interest Declaration – no new conflicts of interest were declared
- C. Approval of Agenda and October Minutes presented by Roger Citron, RPh
 - ACTION: Motion to approve, 2nd, all in favor**
- D. Department Update provided by Trevor Douglass, DC
- E. Mental Health Clinical Advisory Group Update presented by Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

- A. **Quarterly Utilization Report**
- B. **Oncology Prior Authorization (PA) Updates**
Recommendation:
 - Add: Inluriyo™ (imlunestrant) and Keytruda Qlex™ (pembrolizumab + berahyaluronidase alfa-pmph) to Table 1 in the Oncology Agents PA criteria
- C. **Orphan Drug Policy Updates**
Recommendation:
 - Update Table 1 in the Orphan Drugs PA criteria to: support medically appropriate use of Strensiq® (asfotase alfa); Vimizim® (elosulfase alfa); Naglazyme® (galsulfase); Elaprase® (Idursulfase) and Mepsevii™ (vestronidase alfa-vjbk) based on their FDA-approved label; remove drugs for which specific PA criteria are proposed; and update to clarify the high-cost drugs that will be carved out and covered by fee-for-service (FFS).**ACTION: Motion to approve, 2nd, all in favor**

III. DUR ACTIVITIES

- A. **ProDUR Report:** Lan Starkweather, PharmD
- B. **RetroDUR Report:** Dave Engen, PharmD
- C. **Oregon State Drug Review:** Kathy Sentena, PharmD
 - 1. **The Mental Health Clinical Advisory Group**
 - 2. **Pharmacotherapeutic Options for Treating Adolescents with Opioid Use Disorder**
 - 3. **Medication Safety Update**

IV. NEW BUSINESS

- A. **Antifungals Class Update:** Kathy Sentena, PharmD
Recommendations:
 - Make no changes to the PDL based on review of the clinical evidence
 - Evaluate costs in executive session**ACTION: Motion to approve, 2nd, all in favor**
- B. **Epidermolysis Bullosa New Drug Evaluations (NDEs):** Sarah Servid, PharmD
Recommendations:
 - Implement proposed PA criteria for high-cost treatments for epidermolysis bullosa including birch triterpenes, beremagene geperpavec and prademagene zamikeracel
 - Review costs in executive session**Public Comment:** Leland Turner, Chiesi; Keith Dilly, Abeona
ACTION: Motion to approve, 2nd, all in favor
- C. **Carbaglu® (carglumic acid) NDE:** Deanna Moretz, PharmD

Recommendations:

- Make one carglumic acid product preferred on the PDL
- Implement proposed PA criteria to ensure appropriate use
- Evaluate comparative costs in executive session

Public Comment: Andrea Hawkinson, Recordati

ACTION: Motion to approve, 2nd, all in favor

D. Niemann-Pick Type C NDEs: Sara Fletcher, PharmD

Recommendations:

- Make arimoclomol and levacetylleucine non-preferred on the PDL
- Implement proposed PA for high-cost treatments for Niemann-Pick disease type C
- Implement separate miglustat PA for 100 mg formulation with corresponding updates to PA criteria for Pompe Disease and Gaucher disease
- Evaluate comparative costs in executive session

Public Comment: Janelle Raymond, IntraBio

ACTION: Motion to approve, 2nd, all in favor

E. Papzimeos™ (zopapogene imadenovec-drba) NDE: Kathy Sentena, PharmD

Recommendations:

- Designate zopapogene imadenovec-drba as non-preferred on the PDL
- Implement proposed PA criteria to allow coverage for adult patients when other recurrent respiratory papillomatosis treatments have failed

Public Comment: Amber Svardal, Precigen; Andrew Albanese, OHSU

ACTION: Motion to approve, 2nd, all in favor

F. Sohonos® (palovarotene) NDE: Dave Engen, PharmD

Recommendations:

- Designate palovarotene as non-preferred on the PDL
- Implement proposed PA criteria for palovarotene to ensure safe and appropriate use for children and adults with fibrodysplasia ossificans progressiva

ACTION: Motion to approve, 2nd, all in favor

G. Topicals for Inflammatory Skin Disease Class Update with NDE: Deanna Moretz, PharmD

Recommendations:

- Revise PA criteria for the "Topical Agents for Inflammatory Skin Conditions" to include expanded indications for ruxolitinib cream, ruxolitinib foam, roflumilast cream, sirolimus gel, and tapinarof cream
- Maintain delgocitinib cream and make sirolimus topical gel non-preferred on the PDL
- Evaluate comparative costs in executive session

Public Comment: Krystal Ngo, Arcutis Biotherapeutics; Valerie Ng, LEO Pharma; Joe Cirrincione, Incyte

ACTION: Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Tim Langford, PharmD; Cat Livingston, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Jessica Garrison, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. Antifungals Class

Recommendations: Make terbinafine tablets; miconazole (solution & powder); ciclopirox (gel, solution & cream); ketoconazole (shampoo & cream); clotrimazole cream; clotrimazole-betamethasone cream; nystatin-triamcinolone cream; and miconazole 3-day suppository kit preferred. Make all other products non-preferred

ACTION: Motion to approve, 2nd, all in favor

B. Epidermolysis Bullosa

Recommendations: Make Zevaskyn (prademagene zamikeracel), Filsuvez (birch triterpenes) and Vyjuvek (prademagene geperpavec) non-preferred and continue to explore SR offers and VBAs

ACTION: Motion to approve, 2nd, all in favor

C. Carbaglu® (carglumic acid)

Recommendations: Make Carbaglu dispersible tablets preferred and generic carglumic acid non-preferred

ACTION: Motion to approve, 2nd, all in favor

D. Niemann-Pick Type C

Recommendations: Make brand Zavesca tablets preferred

ACTION: Motion to approve, 2nd, all in favor

E. Topicals for Inflammatory Skin Disease

Recommendations: Make no changes to the PDL

ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

Prior Authorization Criteria Update: Oncology

Purpose of the Update:

This update identifies antineoplastic drugs recently approved by the FDA to add to the oncology policy (see **Table 1**).

Table 1. New oncology drugs

<u>Generic Name</u>	<u>Brand Name</u>
sevabertinib	HYRNUO
ziftomenib	KOMZIFTI

Recommendation:

- Update prior authorization criteria to include new, recently approved antineoplastic drugs.

Oncology Agents

Goal(s):

- To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

Length of Authorization:

- Up to 1 year

Requires PA:

- Initiation of therapy for drugs listed in **Table 1** (applies to both pharmacy and provider administered claims). This does not apply to oncologic emergencies administered in an emergency department or during inpatient admission to a hospital.

Covered Populations:

- Elzonris (tatagraxofusp-erzs): FFS and CCO populations beginning 1/1/26
- All others: FFS only

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: National Comprehensive Cancer Network (NCCN) Categories for Recommendations

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
For the 'Uniformed NCCN consensus' defined in Category 1 and 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Strong Panel disagreement regardless of the quality of evidence is a vote of at least 25%.	

Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	Yes: Approve for length of therapy (if specified) or 12 months, (if duration is unspecified).	No: Go to #3
3. Is the request for any continuation of therapy?	Yes: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	No: Go to #4

4. Is the diagnosis funded by OHP?	Yes: Go to #6	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	Yes: Go to #6	No: Pass to RPh. Deny; medical necessity.
6. Is the indication FDA-approved for the requested drug? <u>Note:</u> This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	Yes: Go to #8	No: Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? <u>Note:</u> This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	Yes: Go to #8	No: Go to #9
8. Are there equally or higher recommended alternative agents based on NCCN categories of evidence (Table 1) for the requested indication and place in therapy? Note: When efficacy is similar, the choice of agent should be determined by safety, and then cost. In the absence of a safety concern, the prescriber is expected to use the least costly alternative.	Yes: HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	No: HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).
9. Is there documentation based on chart notes that the patient is enrolled in a	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #10

clinical trial to evaluate efficacy or safety of the requested drug?	Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	
10. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness.
11. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Table 1. Oncology agents which apply to this policy (Updated ~~111/63/20265~~)

New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting.
[Biosimilars for drugs on this list are included in the policy but may not be specifically listed.](#)

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
abiraterone acetate/niraparib tosylate	AKEEGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTTRIF
afamitresgene autoleucel	TECELRA
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVENT
alpelisib	PIQRAY
asciminib	SCSEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia chrysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
avutometinib and defactinib	AVMAPKI FAKZYNJA CO-PACK
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capivasertib	TRUQAP
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA

Generic Name	Brand Name
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
cosibelimab-ipdl	UNLOXCYT
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
datopotamab deruxtecan-dlnk	DATROWAY
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
denileukin diftiox-cxdl	LYMPHIR
dordaviprone	MODEYSO
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
eflornithine	IWILFIN
elacestrant	ORSERDU
elotuzumab	EMPLICITI
elranatamab-bcmm	ELREXFIO
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
ensartinib	ENSACOVE
entrectinib	ROZLYTREK
enzalutamide	XTANDI
epcoritamab-bysp	EPKINLY
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
fruquintinib	FRUZAQLA
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
glofitamab-gxbm	COLUMVI
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
imetelstat	RYTELO

Generic Name	Brand Name
Imlunestrant tosylate	INLURIYO
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lazertinib	LAZCLUZE
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
linvoseltamab-gcpt	LYNOZYFIC
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
melphalan hcl/hepatic delivery kit (HDS)	HEPZATO KIT
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
momelotinib	OJJAARA
mosunetuzumab-axgb	LUNSUMIO
motixafortide	APHEXDA
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
nirogacestat hydrobromide	OGSIVEO
nivolumab	OPDIVO
nivolumab and hyaluronidase-nvhy	OPDIVO QVANTIG
nivolumab; relatlimab-rmbw	OPDUALAG
nogapendekin alfa inbakicept-pmln	ANKTIVA
obecabtagene autoleucel	AUCATZYL
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA

Generic Name	Brand Name
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pembrolizumab;berahyaluronidase alfa-pmph	KEYTRUDA QLEX
pemigatinib	PEMAZYRE
penpulimab-kcqx	none
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidas e-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYX
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
revumenib	REVUFORJ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacituzumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
<u>sevabertinib</u>	<u>HYRNUO</u>
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE

Generic Name	Brand Name
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
sunvozertinib	ZEGFROVY
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
taletrectinib	IBTROZI
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tarlatamab-dlle	IMDELLTRA
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
telisotuzumab vedotin-tllv	EMRELIS
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tislelizumab-jsgr	TEVIMBRA
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
toripalimab-tpzi	LOQTORZI
tovorafenib	OJEMDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trastuzumab-strf	HERCESSI
tremilimumab	IMJUDO
treosulfan	GRAFAPEX
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vimseltinib	ROMVIMZA
vismodegib	ERIVEDGE

Generic Name	Brand Name
vorasidenib	VORANIGO
zanidatamab-hrii	ZIIHERA
zanubrutinib	BRUKINSA
zenocutuzumab-Zbco	BIZENGRI
<u>ziftomenib</u>	<u>KOMZIFTI</u>
ziv-aflibercept	ZALTRAP
zongertinib	HERNEXEOS

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20



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Prior Authorization Criteria Update: Orphan Drug

Purpose of the Update:

This update identifies orphan drugs recently approved by the FDA to add to the orphan drug policy (**Table 1**).

Table 1. Updated orphan drugs

Generic (BRAND) Name

Aficamten (MYQORZO)

Nerandomilast (JASCAYD)

Paltusotine (PALSONIFY)

Recommendation:

- Modify PA criteria to include new orphan drugs.
- Remove drugs for which specific PA criteria is proposed.
- Update PA criteria to clarify the high-cost drugs that will be covered by fee-for-service (FFS).

Appendix 1. Proposed Prior Authorization Criteria

Orphan Drugs

Goal(s):

- To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions
- To limit off-label use of orphan drugs

Length of Authorization:

- Up to 6 months

Requires PA:

- See Table 1 (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Included orphan drugs

Drug	Covered Population
ADAMTS13, recombinant-krhn (ADZYNMA)	FFS
Aficamten (MYQORZO)	FFS
Allogeneic processed thymus tissue-agdc (RETHYMIC)	FFS and CCO populations beginning 1/1/26
Apelisib (VIJOICE)	FFS
Asfotase alfa (STRENSIQ)	FFS and CCO populations beginning 1/1/26
Atidarsagene autotemcel (LENMELDY)	FFS and CCO populations beginning 1/1/26
Avacopan (TAVNEOS)	FFS
Axatilimab-csfr (NIKTIMVO)	FFS
Belumosudil (REZUROCK)	FFS
Burosumab-twza (CRYSVITA)	FFS
Cerliponase alfa (BRINEURA)	FFS
Chenodiol (CTEXLI)	FFS and CCO populations beginning 1/1/26
Crinecefont (CRENESSITY)	FFS
Crovalimab-akkz (PIASKY)	FFS
Danicopan (VOYDEYA)	FFS
Eculizumab (SOLIRIS)	FFS
Eculizumab-aagh (EPYSQLI)	FFS
Eculizumab-aeeb (BKEMV)	FFS
Eladocagene exuparvovec-tneq (KEBILDI)	FFS and CCO populations beginning 1/1/26

Elafibranor (IQIRVO)	FFS
Elapegademase-lvr (REVC0V1)	FFS and CCO populations beginning 1/1/26
Elivaldogene autotemcel (SKYSONA)	FFS and CCO populations beginning 1/1/26
Elosulfase alfa (VIMIZIM)	FFS and CCO populations beginning 1/1/26
Fosdenopterin (NULIBRY)	FFS
Galsulfase (NAGLAZYME)	FFS and CCO populations beginning 1/1/26
Givosiran (GIVLAARI)	FFS
Idursulfase (ELAPRASE)	FFS and CCO populations beginning 1/1/26
Inebilizumab-cdon (UPLIZNA)	FFS
Iptacopan (FABHALTA)	FFS
Leniolisib (JOENJA)	FFS
Levoketoconazole (RECORLEV)	FFS
Lonafarnib (ZOKINVY)	FFS and CCO populations beginning 1/1/26
Lumasiran (OXLUMO)	FFS and CCO populations beginning 1/1/26
Luspatercept (REBLOZYL)	FFS
Maralixibat (LIVMARLI)	FFS and CCO populations beginning 1/1/26
Mavacamten (CAMZYOS)	FFS
Mavorixafor (XOLREMDI)	FFS
Mirdametinib (GOMEKLI)	FFS
Mitapivat (PYRUKYND)	FFS
Nedosiran (RIVFLOZA)	FFS
Nerandomilast (JASCAYD)	FFS
Nipocalimab-aahu (IMAAVY)	FFS
Odevixibat (BYLVAY)	FFS and CCO populations beginning 1/1/26
Olipudase alfa-rpcp (XENPOZYME)	FFS and CCO populations beginning 1/1/26
Palopegteriparatide (YORVIPATH)	FFS
Paltusotine (PALSONIFY)	FFS
Pegcetacoplan (EMPAVELI)	FFS
Plasminogen, human-tvmh (RYPLAZIM)	FFS
Pozelimab-bbfg (VEOPOZ)	FFS and CCO populations beginning 1/1/26
Ravulizumab-cwvz (ULTOMIRIS)	FFS
Remestemcel-L-rknd (RYONCIL)	FFS
Rezafungin (REZZAYO)	FFS
Rozanolixizumab-noli (RYSTIGGO)	FFS
Satralizumab-mwge (ENSPRYNG)	FFS
Seladelpar (LIVDELZI)	FFS
Sodium thiosulfate (PEDMARK)	FFS
Sutimlimab-jome (ENJAYMO)	FFS

Tofersen (QALSODY)	FFS
Trintine tetrahydrochloride (CUVRIOR)	FFS
Velmanase alfa-tycv (LAMZEDE)	FFS and CCO populations beginning 1/1/26
Vestronidase alfa-vjbk (MEPSEVII)	FFS and CCO populations beginning 1/1/26
Zilucoplan (ZILBRYSQ)	FFS

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #4	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	Yes: Go to #4	No: Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in the FDA label (see links in Table 1)? Note: This includes all information required in the FDA-approved indication, including but not limited to, the following as applicable: diagnosis, disease severity, biomarkers, place in therapy, and use as monotherapy or combination therapy.	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	Yes: Go to Renewal Criteria	No: Go to #6

Approval Criteria		
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended baseline and ongoing monitoring parameters described in the FDA label?* *FDA pages for drugs and biologics: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/ approved-cellular-and-gene-therapy-products	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness.
8. Have other therapies been tried and failed?	Yes: Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	No: Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	Yes: Go to #2	No: Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	Yes: Go to #3 Document provider attestation	No: Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	Yes: Go to #4	No: Go to #5

Renewal Criteria		
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	Yes: Approve for up to 6 months Document benefit	No: Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	Yes: Approve for up to 6 months Document benefit and provider attestation	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/25; 6/25; 4/25; 2/25; 12/24; 10/24; 8/24; 4/24; 12/23; 10/23; 6/23; 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20

Implementation: 9/15/25; 5/12/25; 3/10/25; 1/1/25; 9/1/24; 5/1/24; 1/1/24; 11/1/23; 7/1/23; 4/1/23; 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20



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Pharmacy Utilization Summary Report: July 2024 - June 2025

Eligibility	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Total Members (FFS & Encounter)	1,226,816	1,235,264	1,241,007	1,247,678	1,254,503	1,257,986	1,241,274	1,243,854	1,234,473	1,242,572	1,246,331	1,249,863	1,243,468
FFS Members	98,771	97,509	96,865	99,056	99,856	98,868	99,039	93,047	91,577	91,602	90,100	89,262	95,463
OHP Basic with Medicare	8,606	8,437	8,250	8,222	7,915	7,437	7,659	7,451	7,022	6,746	6,382	6,097	7,519
OHP Basic without Medicare	9,308	9,241	9,221	9,278	9,034	8,899	8,472	8,170	8,072	8,028	8,016	7,876	8,635
ACA	80,857	79,831	79,394	81,556	82,907	82,532	82,908	77,426	76,483	76,828	75,702	75,289	79,309
Encounter Members	1,128,045	1,137,755	1,144,142	1,148,622	1,154,647	1,159,118	1,142,235	1,150,807	1,142,896	1,150,970	1,156,231	1,160,601	1,148,006
OHP Basic with Medicare	107,175	107,413	106,294	103,103	98,130	90,342	82,625	80,472	75,440	76,700	77,380	77,913	90,249
OHP Basic without Medicare	66,835	66,785	66,566	66,469	66,271	65,605	64,002	63,793	62,866	62,847	62,790	62,724	64,796
ACA	954,035	963,557	971,282	979,050	990,246	1,003,171	995,608	1,006,542	1,004,590	1,011,423	1,016,061	1,019,964	992,961

Gross Cost Figures for Drugs	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	YTD Sum
Total Amount Paid (FFS & Encounter)	\$132,160,636	\$130,407,285	\$128,296,462	\$141,572,425	\$126,844,169	\$139,444,267	\$145,920,046	\$132,492,369	\$148,003,833	\$150,392,854	\$146,777,578	\$147,211,663	\$1,669,523,586
Mental Health Carve-Out Drugs	\$12,108,246	\$11,876,191	\$11,493,038	\$13,459,508	\$11,704,615	\$14,415,165	\$14,620,898	\$13,505,172	\$14,851,170	\$15,614,328	\$15,274,033	\$15,635,947	\$164,558,312
OHP Basic with Medicare	\$3,424	\$76	\$6,734	\$10,098	\$9,432	\$1,264	\$6,525	\$5,748	\$2,268	\$5,567	\$8,358	\$10,675	\$70,169
OHP Basic without Medicare	\$4,268,712	\$4,211,876	\$4,019,845	\$4,500,610	\$3,944,225	\$4,744,989	\$4,547,643	\$4,597,080	\$5,044,491	\$4,923,201	\$4,721,568	\$4,596,029	\$54,120,271
ACA	\$6,799,278	\$6,621,741	\$6,575,688	\$7,603,453	\$6,779,982	\$8,386,186	\$8,532,090	\$7,517,012	\$8,474,840	\$9,005,276	\$8,724,906	\$8,758,876	\$93,779,329
FFS Physical Health Drugs	\$2,495,306	\$2,251,045	\$2,292,703	\$2,160,929	\$1,777,472	\$2,156,677	\$2,390,056	\$2,251,098	\$2,215,439	\$2,260,280	\$2,254,652	\$2,122,760	\$26,628,417
OHP Basic with Medicare	\$32,196	\$29,391	\$27,882	\$30,120	\$27,308	\$28,640	\$29,726	\$28,857	\$27,392	\$26,157	\$24,643	\$23,138	\$335,450
OHP Basic without Medicare	\$749,985	\$648,776	\$677,035	\$660,666	\$540,675	\$642,047	\$678,897	\$705,072	\$664,963	\$718,207	\$654,374	\$596,544	\$7,937,240
ACA	\$1,510,864	\$1,413,528	\$1,404,585	\$1,327,807	\$1,065,971	\$1,282,350	\$1,372,539	\$1,218,140	\$1,281,407	\$1,245,636	\$1,302,335	\$1,192,275	\$15,617,436
FFS Physician Administered Drugs	\$1,300,458	\$1,518,262	\$923,560	\$1,361,959	\$1,611,340	\$1,250,650	\$1,800,570	\$1,664,207	\$1,516,355	\$1,728,301	\$1,127,540	\$952,930	\$16,756,131
OHP Basic with Medicare	\$127,195	\$163,013	\$131,847	\$132,502	\$86,148	\$123,545	\$144,386	\$87,070	\$120,993	\$113,750	\$60,505	\$72,595	\$1,363,549
OHP Basic without Medicare	\$192,566	\$295,895	\$53,301	\$313,764	\$432,161	\$191,592	\$236,124	\$104,311	\$355,792	\$293,199	\$167,273	\$114,459	\$2,750,438
ACA	\$421,952	\$475,672	\$463,173	\$503,412	\$614,921	\$532,339	\$758,063	\$573,858	\$408,817	\$608,842	\$341,473	\$326,322	\$6,028,844
Encounter Physical Health Drugs	\$87,543,228	\$86,325,448	\$86,459,140	\$93,156,186	\$84,761,785	\$90,906,200	\$92,893,909	\$86,087,784	\$95,296,057	\$97,592,204	\$95,969,111	\$93,361,563	\$1,090,352,614
OHP Basic with Medicare	\$391,042	\$390,491	\$398,007	\$429,484	\$352,769	\$334,681	\$368,020	\$337,457	\$355,256	\$382,503	\$373,055	\$346,527	\$4,459,293
OHP Basic without Medicare	\$19,157,031	\$18,827,273	\$17,944,974	\$19,634,207	\$17,566,872	\$18,915,414	\$19,324,853	\$17,085,554	\$18,639,646	\$19,002,447	\$18,042,481	\$17,690,553	\$221,831,305
ACA	\$57,111,891	\$56,628,124	\$57,535,903	\$61,319,839	\$56,103,719	\$60,505,861	\$60,636,038	\$56,571,698	\$62,558,865	\$64,382,712	\$63,591,033	\$61,179,720	\$718,125,402
Encounter Physician Administered Drugs	\$28,713,397	\$28,436,340	\$27,128,021	\$31,433,843	\$26,988,957	\$30,715,576	\$34,214,613	\$28,984,108	\$34,124,811	\$33,197,741	\$32,152,242	\$35,138,463	\$371,228,112
OHP Basic with Medicare	\$1,091,319	\$1,008,440	\$971,586	\$1,129,581	\$801,494	\$801,219	\$1,157,258	\$804,840	\$758,640	\$824,445	\$724,763	\$713,309	\$10,786,896
OHP Basic without Medicare	\$6,253,229	\$6,151,513	\$5,444,588	\$6,360,472	\$5,343,141	\$5,793,715	\$5,662,636	\$5,910,499	\$9,415,729	\$6,043,170	\$5,912,843	\$5,874,448	\$74,165,984
ACA	\$18,035,790	\$17,819,546	\$17,008,139	\$19,895,387	\$17,633,831	\$19,777,242	\$22,911,282	\$17,485,364	\$18,988,410	\$20,561,312	\$19,768,241	\$22,930,857	\$232,815,399

OHP = Oregon Health Plan

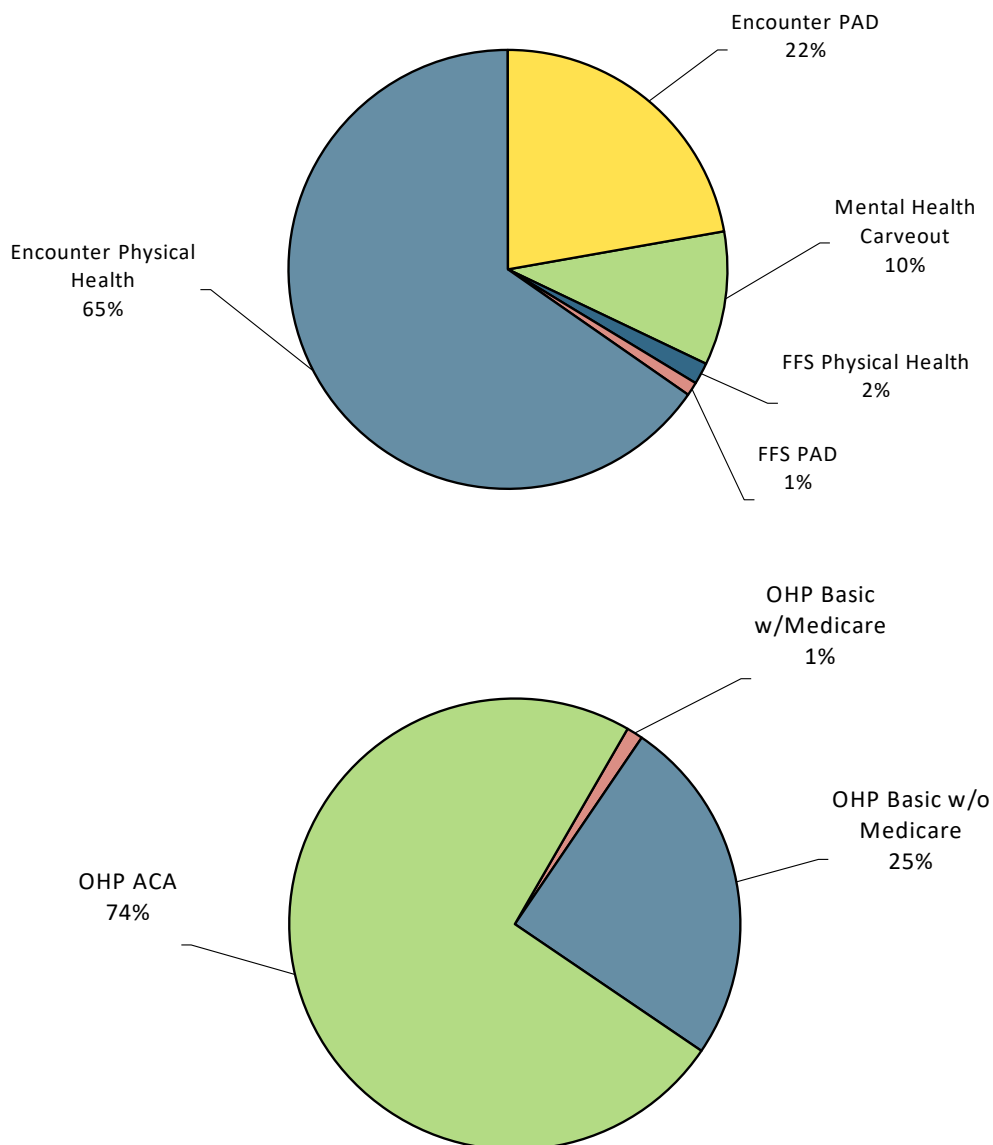
ACA = Affordable Care Act expansion

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 17, 2026

Pharmacy Utilization Summary Report: July 2024 - June 2025

YTD Percent Paid Amounts



OHP = Oregon Health Plan

ACA = Affordable Care Act expansion

PAD = Physician-administered drugs

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.

If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 17, 2026

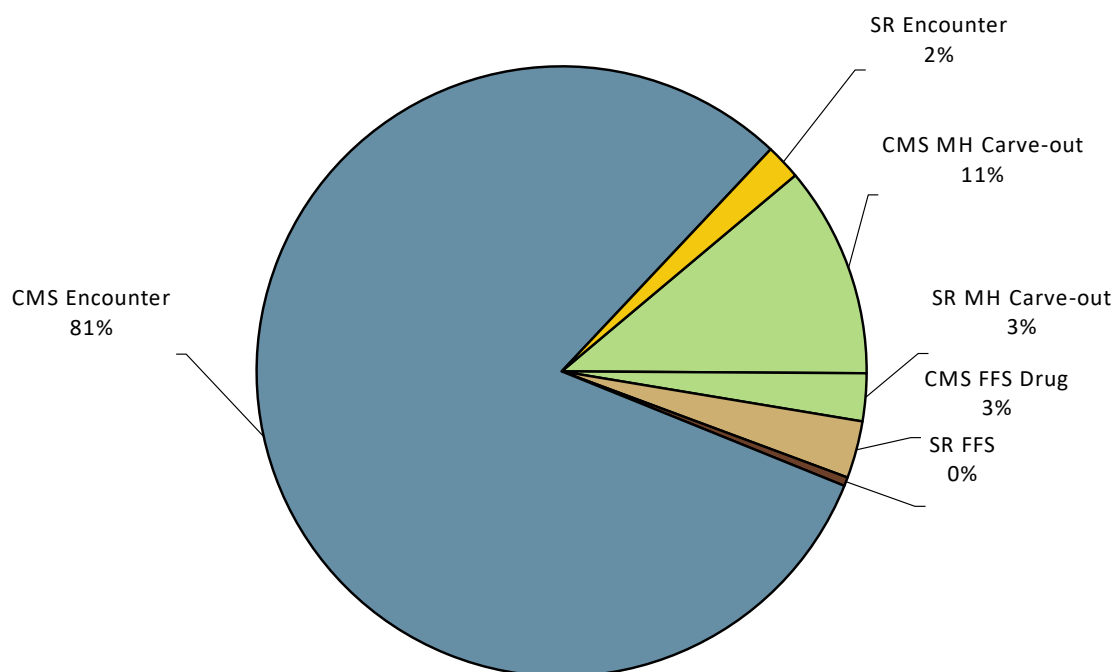


Pharmacy Utilization Summary Report: July 2024 - June 2025

Quarterly Rebates Invoiced	2024-Q3	2024-Q4	2025-Q1	2025-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	\$116,953,793	\$119,367,641	\$136,316,202	\$137,659,267	\$510,296,903
CMS MH Carve-out	\$12,780,546	\$13,564,774	\$15,447,598	\$15,406,762	\$57,199,680
SR MH Carve-out	\$2,915,315	\$3,354,368	\$3,055,632	\$3,579,531	\$12,904,846
CMS FFS Drug	\$4,185,987	\$3,278,456	\$4,222,441	\$3,778,521	\$15,465,405
SR FFS	\$508,647	\$481,787	\$651,850	\$736,281	\$2,378,565
CMS Encounter	\$93,564,912	\$95,614,931	\$111,307,781	\$112,306,159	\$412,793,783
SR Encounter	\$2,998,386	\$3,073,325	\$1,630,900	\$1,852,013	\$9,554,624

Quarterly Net Drug Costs	2024-Q3	2024-Q4	2025-Q1	2025-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	\$273,910,590	\$288,493,220	\$290,100,046	\$306,722,828	\$1,159,226,683
Mental Health Carve-Out Drugs	\$19,781,615	\$22,660,145	\$24,474,011	\$27,538,015	\$94,453,785
FFS Phys Health + PAD	\$6,086,700	\$6,558,783	\$6,963,433	\$5,931,662	\$25,540,578
Encounter Phys Health + PAD	\$248,042,276	\$259,274,291	\$258,662,602	\$273,253,151	\$1,039,232,320

YTD Percent Rebates Invoiced



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

Last Updated: January 17, 2026



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Pharmacy Utilization Summary Report: July 2024 - June 2025

Gross PMPM Drug Costs (Rebates not Subtracted)													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	\$107.73	\$105.57	\$103.38	\$113.47	\$101.11	\$110.85	\$117.56	\$106.52	\$119.89	\$121.03	\$117.77	\$117.78	\$111.89
Mental Health Carve-Out Drugs	\$9.87	\$9.61	\$9.26	\$10.79	\$9.33	\$11.46	\$11.78	\$10.86	\$12.03	\$12.57	\$12.26	\$12.51	\$11.03
FFS Physical Health Drugs	\$25.26	\$23.09	\$23.67	\$21.82	\$17.80	\$21.81	\$24.13	\$24.19	\$24.19	\$24.68	\$25.02	\$23.78	\$23.29
FFS Physician Administered Drugs	\$13.17	\$15.57	\$9.53	\$13.75	\$16.14	\$12.65	\$18.18	\$17.89	\$16.56	\$18.87	\$12.51	\$10.68	\$14.62
Encounter Physical Health Drugs	\$77.61	\$75.87	\$75.57	\$81.10	\$73.41	\$78.43	\$81.33	\$74.81	\$83.38	\$84.79	\$83.00	\$80.44	\$79.14
Encounter Physician Administered Drugs	\$25.45	\$24.99	\$23.71	\$27.37	\$23.37	\$26.50	\$29.95	\$25.19	\$29.86	\$28.84	\$27.81	\$30.28	\$26.94
Claim Counts													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Total Claim Count (FFS & Encounter)	1,280,032	1,251,239	1,238,639	1,339,861	1,233,811	1,319,063	1,369,962	1,242,925	1,354,754	1,379,301	1,364,510	1,319,182	1,307,773
Mental Health Carve-Out Drugs	213,698	208,391	205,171	222,216	204,497	221,231	229,272	209,597	228,441	230,329	227,780	224,414	218,753
FFS Physical Health Drugs	28,226	25,562	25,271	26,880	24,305	26,412	29,491	26,292	27,642	27,281	25,851	24,582	26,483
FFS Physician Administered Drugs	8,712	8,212	8,012	8,381	7,282	7,819	9,983	8,789	8,886	8,872	8,591	8,152	8,474
Encounter Physical Health Drugs	895,799	876,837	872,536	941,603	866,204	926,625	955,293	863,283	946,936	962,790	950,540	915,665	914,509
Encounter Physician Administered Drugs	133,597	132,237	127,649	140,781	131,523	136,976	145,923	134,964	142,849	150,029	151,748	146,369	139,554
Gross Amount Paid per Claim (Rebates not Subtracted)													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Average Paid / Claim (FFS & Encounter)	\$103.25	\$104.22	\$103.58	\$105.66	\$102.81	\$105.71	\$106.51	\$106.60	\$109.25	\$109.04	\$107.57	\$111.59	\$106.32
Mental Health Carve-Out Drugs	\$56.66	\$56.99	\$56.02	\$60.57	\$57.24	\$65.16	\$63.77	\$64.43	\$65.01	\$67.79	\$67.06	\$69.67	\$62.53
FFS Physical Health Drugs	\$88.40	\$88.06	\$90.72	\$80.39	\$73.13	\$81.66	\$81.04	\$85.62	\$80.15	\$82.85	\$87.22	\$86.35	\$83.80
FFS Physician Administered Drugs	\$149.27	\$184.88	\$115.27	\$162.51	\$221.28	\$159.95	\$180.36	\$189.35	\$170.65	\$194.80	\$131.25	\$116.90	\$164.71
Encounter Physical Health Drugs	\$97.73	\$98.45	\$99.09	\$98.93	\$97.85	\$98.10	\$97.24	\$99.72	\$100.64	\$101.36	\$100.96	\$101.96	\$99.34
Encounter Physician Administered Drugs	\$214.93	\$215.04	\$212.52	\$223.28	\$205.20	\$224.24	\$234.47	\$214.75	\$238.89	\$221.28	\$211.88	\$240.07	\$221.38
Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	\$22.69	\$22.85	\$22.86	\$22.56	\$22.11	\$22.30	\$22.19	\$22.27	\$22.63	\$22.88	\$22.70	\$23.12	\$22.60
Mental Health Carve-Out Drugs	\$14.47	\$14.43	\$14.40	\$14.35	\$14.19	\$15.29	\$15.76	\$16.27	\$15.73	\$16.79	\$15.54	\$15.61	\$15.24
FFS Physical Health Drugs	\$21.65	\$23.80	\$24.72	\$21.60	\$21.63	\$20.80	\$22.43	\$22.70	\$23.23	\$22.45	\$23.82	\$24.08	\$22.74
Encounter Physical Health Drugs	\$24.83	\$24.98	\$24.99	\$24.71	\$24.16	\$24.14	\$23.84	\$23.82	\$24.41	\$24.46	\$24.50	\$25.06	\$24.49
Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	\$812.54	\$801.49	\$712.59	\$725.96	\$751.81	\$816.38	\$828.30	\$867.17	\$867.66	\$873.77	\$881.89	\$881.51	\$818.42
Mental Health Carve-Out Drugs	\$1,586.25	\$1,593.41	\$1,556.90	\$1,689.50	\$1,594.12	\$1,780.19	\$1,732.97	\$1,722.67	\$1,726.17	\$1,770.49	\$1,750.80	\$1,801.58	\$1,692.09
FFS Physical Health Drugs	\$497.82	\$468.02	\$429.55	\$437.81	\$401.30	\$479.65	\$476.83	\$506.23	\$473.10	\$496.52	\$506.98	\$505.65	\$473.29
Encounter Physical Health Drugs	\$775.82	\$764.57	\$677.22	\$680.77	\$713.61	\$764.07	\$780.17	\$820.64	\$820.55	\$823.13	\$830.81	\$824.14	\$772.96
Generic Drug Use Percentage													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Generic Drug Use Percentage	91.5%	91.3%	90.1%	90.2%	90.7%	91.3%	91.5%	91.7%	91.6%	91.6%	91.7%	91.6%	91.2%
Mental Health Carve-Out Drugs	97.3%	97.3%	97.3%	97.2%	97.3%	97.2%	97.2%	97.2%	97.1%	97.1%	97.0%	97.0%	97.2%
FFS Physical Health Drugs	86.0%	85.5%	83.7%	85.9%	86.4%	86.7%	87.1%	87.0%	87.3%	87.3%	86.9%	87.1%	86.4%
Encounter Physical Health Drugs	90.3%	90.1%	88.6%	88.7%	89.3%	90.0%	90.3%	90.5%	90.4%	90.4%	90.5%	90.4%	90.0%
Preferred Drug Use Percentage													
	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Avg Monthly
Preferred Drug Use Percentage	88.88%	88.58%	88.53%	88.48%	88.41%	88.34%	88.44%	88.42%	88.46%	88.49%	88.48%	88.51%	88.5%
Mental Health Carve-Out Drugs	86.71%	86.67%	86.51%	86.49%	86.52%	86.36%	86.28%	86.34%	86.27%	86.30%	86.29%	86.37%	86.4%
FFS Physical Health Drugs	94.55%	94.61%	94.34%	94.49%	94.67%	94.57%	94.41%	93.69%	94.21%	94.38%	93.96%	94.10%	94.3%
Encounter Physical Health Drugs	89.26%	88.89%	88.88%	88.81%	88.72%	88.67%	88.81%	88.80%	88.86%	88.87%	88.89%	88.92%	88.9%

Amount Paid on the Claim = 1) Ingredient Cost ((AAAC/NADAC/WAC) x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: January 17, 2026



Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
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College of Pharmacy

Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	VRAYLAR*	Antipsychotics, 2nd Gen	\$6,944,194	13.2%	4,951	\$1,403	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	\$6,102,848	11.6%	2,217	\$2,753	Y
3	REXULTI*	Antipsychotics, 2nd Gen	\$3,468,093	6.6%	2,480	\$1,398	V
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	\$3,041,882	5.8%	1,223	\$2,487	Y
5	CAPLYTA*	Antipsychotics, 2nd Gen	\$2,158,511	4.1%	1,440	\$1,499	V
6	SPRAVATO*	Antidepressants	\$1,948,901	3.7%	1,448	\$1,346	V
7	INVEGA TRINZA	Antipsychotics, Parenteral	\$1,618,309	3.1%	196	\$8,257	Y
8	ARISTADA	Antipsychotics, Parenteral	\$1,262,935	2.4%	498	\$2,536	Y
9	AUVELITY	Antidepressants	\$1,174,521	2.2%	1,211	\$970	V
10	TRINTELLIX	Antidepressants	\$1,148,683	2.2%	2,438	\$471	V
11	LYBALVI*	Antipsychotics, 2nd Gen	\$851,752	1.6%	582	\$1,463	V
12	BUPROPION XL	Antidepressants	\$825,868	1.6%	60,454	\$14	Y
13	ABILIFY ASIMTUFII	Antipsychotics, Parenteral	\$800,080	1.5%	151	\$5,299	Y
14	SERTRALINE HCL	Antidepressants	\$726,895	1.4%	62,717	\$12	Y
15	QELBREE*	ADHD Drugs	\$681,433	1.3%	1,414	\$482	Y
16	TRAZODONE HCL	Antidepressants	\$670,516	1.3%	55,237	\$12	V
17	DULOXETINE HCL	Antidepressants	\$631,493	1.2%	39,446	\$16	Y
18	FLUOXETINE HCL	Antidepressants	\$624,613	1.2%	48,682	\$13	Y
19	ESCITALOPRAM OXALATE	Antidepressants	\$619,031	1.2%	48,755	\$13	Y
20	INVEGA HAFYERA	Antipsychotics, Parenteral	\$426,283	0.8%	25	\$17,051	Y
21	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	\$425,531	0.8%	32,481	\$13	
22	LAMOTRIGINE	Antiepileptics, Outpatient	\$419,503	0.8%	33,640	\$12	Y
23	DAYBUE*	STC 99 - Miscellaneous	\$358,487	0.7%	12	\$29,874	N
24	ARIPIRAZOLE*	Antipsychotics, 2nd Gen	\$343,149	0.7%	23,825	\$14	Y
25	BIKTARVY	HIV	\$329,648	0.6%	96	\$3,434	Y
26	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	\$287,126	0.5%	22,088	\$13	Y
27	UZEDY	Antipsychotics, Parenteral	\$285,897	0.5%	98	\$2,917	Y
28	ATOMOXETINE HCL*	ADHD Drugs	\$257,481	0.5%	10,935	\$24	Y
29	VENLAFAXINE HCL ER	Antidepressants	\$248,515	0.5%	17,811	\$14	Y
30	Inj, Nusinersen, 0.1mg	Physican Administered Drug	\$246,012	0.5%	1	\$246,012	
31	SERTRALINE HCL	Antidepressants	\$240,661	0.5%	1,547	\$156	V
32	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	\$226,127	0.4%	18	\$12,563	Y
33	COBENFY*	Antipsychotics, 2nd Gen	\$223,324	0.4%	146	\$1,530	V
34	MIRTAZAPINE	Antidepressants	\$221,795	0.4%	14,853	\$15	Y
35	OLANZAPINE*	Antipsychotics, 2nd Gen	\$206,958	0.4%	14,408	\$14	Y
36	GUANFACINE HCL ER	ADHD Drugs	\$206,450	0.4%	14,643	\$14	Y
37	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	\$193,304	0.4%	309	\$626	N
38	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	\$191,737	0.4%	97	\$1,977	Y
39	LAMOTRIGINE ER	Antiepileptics, Outpatient	\$181,739	0.3%	5,147	\$35	V
40	Inj Pembrolizumab	Physican Administered Drug	\$181,237	0.3%	56	\$3,236	
* Drug requires Prior Authorization							
Top 40 Aggregate:			\$41,001,524		527,776	\$8,750	
All FFS Drugs Totals:			\$52,681,300		772,975	\$666	

Notes

- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ((AAAC/NADAC/WAC) x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount



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College of Pharmacy

Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2025

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	BIKTARVY	HIV	\$329,648	3.9%	96	\$3,434	Y
2	Inj, Nusinersen, 0.1mg	Physican Administered Drug	\$246,012	2.9%	1	\$246,012	
3	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	\$226,127	2.7%	18	\$12,563	Y
4	OZEMPIC*	Diabetes, GLP-1 Receptor Agonists and GIP The	\$193,304	2.3%	309	\$626	N
5	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	\$191,737	2.3%	97	\$1,977	Y
6	Inj Pembrolizumab	Physican Administered Drug	\$181,237	2.1%	56	\$3,236	
7	JARDIANCE	Diabetes, SGLT-2 Inhibitors	\$139,303	1.6%	380	\$367	Y
8	ELIQUIS	Anticoagulants, Oral and SQ	\$136,014	1.6%	347	\$392	Y
9	MOUNJARO*	Diabetes, GLP-1 Receptor Agonists and GIP The	\$117,327	1.4%	168	\$698	N
10	EVEROLIMUS*	Antineoplastics, Newer	\$116,343	1.4%	13	\$8,949	
11	EPIDIOLEX*	Antiepileptics, Outpatient	\$114,840	1.4%	55	\$2,088	N
12	Inj Fam-Trastu Deru-Nxki 1mg	Physican Administered Drug	\$114,446	1.4%	7	\$16,349	
13	TRIKAFTA*	Cystic Fibrosis	\$111,744	1.3%	14	\$7,982	N
14	SKYRIZI ON-BODY*	Targeted Immune Modulators	\$110,697	1.3%	11	\$10,063	N
15	TRULICITY*	Diabetes, GLP-1 Receptor Agonists and GIP The	\$102,808	1.2%	145	\$709	Y
16	BRIXADI	Substance Use Disorders, Opioid & Alcohol	\$101,213	1.2%	66	\$1,534	Y
17	IMCIVREE*	Weight Management Drugs	\$98,328	1.2%	3	\$32,776	
18	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	\$89,146	1.1%	10	\$8,915	
19	STELARA*	Targeted Immune Modulators	\$88,100	1.0%	4	\$22,025	N
20	Sacituzumab Govitecan-Hziy	Physican Administered Drug	\$78,358	0.9%	16	\$4,897	
21	EMVERM	STC 31 - Antiparasitics	\$74,672	0.9%	3	\$24,891	
22	WINREVAIR*	Pulmonary Arterial Hypertension Parenteral Dri	\$74,313	0.9%	5	\$14,863	N
23	KISQALI*	Antineoplastics, Newer	\$71,898	0.9%	6	\$11,983	
24	HUMIRA(CF) PEN*	Targeted Immune Modulators	\$70,757	0.8%	13	\$5,443	Y
25	FINTEPLA*	Antiepileptics, Outpatient	\$66,430	0.8%	5	\$13,286	N
26	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	\$61,043	0.7%	951	\$64	Y
27	SLYND	Contraceptives	\$58,643	0.7%	196	\$299	
28	DEXCOM G7 SENSOR*	Diabetic Supplies, CGM	\$58,212	0.7%	253	\$230	Y
29	Injection, Nivolumab	Physican Administered Drug	\$57,015	0.7%	27	\$2,112	
30	RINVOQ*	Targeted Immune Modulators	\$55,779	0.7%	19	\$2,936	N
31	COSENTYX SENSOREADY (2 PENS)*	Targeted Immune Modulators	\$54,727	0.6%	7	\$7,818	N
32	LISDEXAMFETAMINE DIMESYLATE*	ADHD Drugs	\$54,343	0.6%	855	\$64	Y
33	Inj., Cemiplimab-Rwlc, 1 Mg	Physican Administered Drug	\$49,989	0.6%	9	\$5,554	
34	IBRANCE*	Antineoplastics, Newer	\$49,416	0.6%	3	\$16,472	
35	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	\$49,160	0.6%	1,856	\$26	Y
36	Inj, Faricimab-Svoa, 0.1mg	Physican Administered Drug	\$48,842	0.6%	85	\$575	
37	CREON	Pancreatic Enzymes	\$48,412	0.6%	43	\$1,126	Y
38	ENBREL SURECLICK*	Targeted Immune Modulators	\$48,300	0.6%	13	\$3,715	Y
39	SYMBICORT	Corticosteroids/Beta-Agonist Combination, Inh:	\$46,687	0.6%	218	\$214	Y
40	Altuviiio Per Factor Viii lu	Physican Administered Drug	\$46,642	0.6%	2	\$23,321	
Top 40 Aggregate:			\$4,032,011		6,385	\$13,015	
All FFS Drugs Totals:			\$8,455,265		87,723	\$649	

* Drug requires Prior Authorization

Notes

- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lo wer, pay Billed Amount, 2) - TPL amount

ProDUR Report for October through December 2025
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	0	0	0	0	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,119	537	0	1,581	1.2%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	8,918	2,571	0	6,339	5.0%	N/A
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	109,617	23,665	81	85,871	62.0%	21.6%
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	42,094	11,506	0	30,553	23.8%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	863	192	0	669	0.4%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	4	2	0	2	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	811	227	0	582	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	373	134	0	239	0.1%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	7	4	0	3	0.0%	N/A
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	192	77	0	115	0.1%	40.1%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	11,739	3,559	0	8,166	6.6%	N/A
		Totals	176,737					

ProDUR Report for October through December 2025
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	8,319	1,722	6,597	94,383	8.8%	20.7%
ER	Lexapro (Escitalopram)	6,509	1,214	5,295	67,308	9.6%	18.7%
ER	Prozac (Fluoxetine)	6,352	1,245	5,107	69,148	9.1%	19.6%
ER	Celexa (Citalopram)	1,698	308	1,390	20,703	8.1%	18.1%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	9,921	1,802	8,119	106,152	9.3%	18.2%
ER	Trazodone	7,789	1,719	6,070	75,590	10.3%	22.1%
ER	Cymbalta (Duloxetine)	5,668	1,170	4,498	54,499	10.4%	20.6%
ER	Effexor (Venlafaxine)	2,972	548	2,424	31,020	9.6%	18.4%
ER	Remeron (Mirtazapine)	2,483	497	1,986	20,811	11.9%	20.0%
ER	Elavil (Amitriptyline)	1,781	384	1,397	18,414	9.6%	21.6%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,298	1,317	3,981	37,934	13.9%	24.9%
ER	Abilify (Aripiprazole)	4,619	893	3,726	35,900	12.8%	19.3%
ER	Zyprexa (Olanzapine)	3,043	817	2,226	23,134	13.1%	26.8%
ER	Risperdal (Risperidone)	2,170	534	1,636	14,993	14.4%	24.6%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,525	878	3,647	45,691	9.8%	19.4%
ER	Lorazepam	284	86	198	12,145	2.3%	30.3%
ER	Alprazolam	201	52	149	7,095	2.8%	25.9%
ER	Diazepam	98	24	74	4,366	2.2%	24.5%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	7,696	1,638	6,058	58,507	13.1%	21.3%
ER	Intuniv (Guanfacine ER)	2,391	388	2,003	20,601	11.6%	16.2%
ER	Depakote (Divalproex)	1,766	533	1,233	13,150	13.3%	30.2%
ER	Suboxone (Buprenorphine/Naloxone)	71	27	44	1,422	4.9%	38.0%

ProDUR Report for October through December 2025
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC- Other
ER	October	6,366	166	234	728	27	4,946	21	7	237
ER	November	4,978	145	228	743	3	3,628	14	1	216
ER	December	5,111	221	257	624	4	3,718	23	0	264
	Total	16,455	532	719	2,095	34	12,292	58	8	717
	Percentage of Total Overrides		3.2%	4.4%	12.7%	0.2%	74.7%	0.4%	0.0%	4.4%

ProDUR Report for October through December 2025			
DUR Alert Cost Savings Report			
Month	Alert Type	Prescriptions Not Dispensed	Cost Savings
October	DD	47	\$4,966.82
	ER	151	\$36,019.95
	HD	1	\$5.99
	ID	29	\$7,564.46
	LR	1	\$191.88
	MC	2	\$437.41
	TD	6	\$1,030.93
	October Total	237	\$50,217.44
November	DD	52	\$29,540.29
	ER	445	\$140,491.15
	HD	5	\$149.00
	ID	54	\$13,922.12
	LR	2	\$193.94
	MX	1	\$56.17
	TD	9	\$28,827.54
	November Total	568	\$213,180.21
December	DD	24	\$2,399.99
	ER	86	\$12,372.14
	ID	19	\$3,792.90
	TD	1	\$1,295.72
	December Total	130	\$19,860.75
Total 4Q2025 Savings			\$283,258.40

Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Billing Correction Review	High Cost OCC 3	Total Patients Identified	66	9		
		Total Claims Identified	66	10		
		Claims reviewed	14			
		Estimated Savings	\$0			
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	7			
		Total Claims Identified	7			
		Claims reviewed	1			
		Estimated Savings	\$0			
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	1		
		Total Claims Identified	7	1		
		Claims reviewed	2			
		Estimated Savings	\$0			
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	8			
		Total Claims Identified	9			
		Claims reviewed	3			
		Estimated Savings	\$0			



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	23	1		
		Unique Patients Identified	24	1		
		Total Faxes Successfully Sent	20	1		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	2			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	\$1,790			
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	132	25		
		Unique Patients Identified	138	26		
		Total Faxes Successfully Sent	105	23		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	33	3		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	\$15,286	\$586		



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	965			
		High risk patients identified	4			
		Prescribers successfully notified	2			
		Patients with continued antipsychotic therapy in the following 90 days	1			



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	32	13		
		Total prescribers identified	31	13		
		Prescribers successfully notified	31			
		Patients with claims for the same antipsychotic within the next 90 days	11			
		Patients with claims for a different antipsychotic within the next 90 days	1			



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	65			
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	24			
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	150	1		
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	37			
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	28			
		Letters Sent To Providers	19			
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28			
		Letters Sent To Providers	29			
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	26			
		Letters Sent To Providers	10			
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	26			
		Letters Sent To Providers	8			
	Lock-In	RetroDUR Profiles Reviewed	7			
		Locked In	0			



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	34	2		
		Total prescribers identified	32	2		
		Prescribers successfully notified	25			
		Patients with paid claims within next 60 days	16			
		Patients with denied claim within next 60 days	11			



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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	53	12		
		Total prescribers identified	53	12		
		Prescribers successfully notified	52	10		
		Patients with discontinuation of therapy within next 90 days	22	10		
		Patients with new prescription for naloxone within next 90 days	4			
		Average number of sedative drugs dispensed within next 90 days	13	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	13	0		
	Oncology Denials	Total patients identified	1			
		Total prescribers identified	1			
		Prescribers successfully notified	1			
	TCAs in Children	TCA Denials in Children	23	1		
		Total patients identified	6			
		Total prescribers identified	6			
		Prescribers successfully notified	3			
		Patients with claims for a TCA within the next 90 days	3			

New Therapies for Treatment of Chronic Obstructive Pulmonary Disease

Deanna Moretz, PharmD, BCPS, Oregon State University Drug Use Research and Management Group

Approximately 10% of individuals who are 40 years of age or older have Chronic Obstructive Pulmonary Disease (COPD).¹ In the United States, COPD is consistently ranked among the top causes of death, with mortality rates of more than 120,000 individuals each year.² As a result, COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic therapy.³

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) annually updates guidance for the management of COPD. The 2023 guideline included revised strategies for pharmacologic COPD treatment based upon new Gold Group Classifications.⁵ In addition, recommendations for the use of triple inhaler therapy in the updated GOLD "ABE" groups was introduced with the 2023 guidance.⁵ Since the publication of that guideline, 2 new therapies have received Food and Drug Administration (FDA) approval for maintenance treatment of COPD. This newsletter will review the evidence for these therapies and discuss their role in COPD management. The 2025 GOLD guidance will also be briefly reviewed to describe the place in therapy for the 2 new COPD treatments.

Assessment of COPD Treatments

Outcomes to assess the effectiveness of COPD therapies include changes in lung function, quality of life, dyspnea, COPD exacerbation rate and/or severity, and frequency of adverse events. The most common surrogate outcome used in studies to determine treatment effectiveness is post-bronchodilator forced expiratory volume in one second (FEV₁).⁵ The minimal clinically important difference (MCID) in FEV₁ values for COPD changes have not been clearly defined, but research in COPD patients suggest that the minimally important FEV₁ change is 120 mL.⁵ The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on quality of life (QoL) with scores ranging from 0 to 100.⁶ Higher scores on the SGRQ indicate more QoL limitations.⁶ The MCID on the SGRQ is an improvement of 4 points.⁶

Treatment of COPD

Goals of COPD therapy include symptom relief, improved exercise tolerance, slowed disease progression, and reduced exacerbations. The GOLD report uses the core metrics of dyspnea severity and frequency of exacerbations to categorize patients into GOLD "ABE" groups for initial pharmacologic management.⁵ For patients in Group A (mild COPD), therapy should be initiated with a short-acting or long-acting bronchodilator.⁵ Patients with more severe COPD in Group B

should be started on combined long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhaler therapy.⁵ For patients in Group E (severe COPD with frequent exacerbations), an inhaled corticosteroid (ICS) may be added to LABA/LAMA therapy if blood eosinophils are greater than 300 cells/ μ L.⁵ Long-term monotherapy with a ICS is not recommended, and triple LABA/LAMA/ICS inhaler therapy is preferred over LABA/ICS therapy to minimize adverse events associated with steroid therapy.⁵

Roflumilast, an oral phosphodiesterase (PDE)-4 inhibitor, is FDA-approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.⁷ Data show that roflumilast may have greater benefit in patients with a prior history of hospitalization for an acute COPD exacerbation.⁵ The 2023 GOLD guidance provides an algorithm for follow-up pharmacologic treatment where management is based on 2 key treatable traits: persistence of dyspnea and occurrence of exacerbations.⁵ Roflumilast is included in this algorithm for COPD patients who are adequately treated with LABA/LAMA/ICS therapy, but continue to have yearly exacerbations, FEV₁ less than or equal to 50%, and chronic bronchitis.⁵

The GOLD guidance recommends the use of roflumilast as add-on maintenance therapy to prevent exacerbations; it is not recommended for improvement in other COPD outcomes.⁵ In the Fee-for-Service (FFS) Oregon Health Plan (OHP), providers must submit a prior authorization (PA) request to ensure oral roflumilast is prescribed for patients with severe or very severe COPD, chronic bronchitis and yearly exacerbations despite treatment with an ICS and long-acting inhaler treatment (LABA or LAMA).

New COPD Therapy: OHTUVAYRE (Ensifentrine)

In June 2024, ensifentrine, a dual PDE-3 and PDE-4 inhibitor, received FDA-approval for maintenance treatment of COPD in adults at a dose of 3 mg by inhaled jet nebulizer twice daily.⁸ Due to dual inhibition of PDE, ensifentrine has anti-inflammatory activity and bronchodilator effects.⁸ It is not indicated for use as rescue therapy for immediate relief during a COPD exacerbation.⁸ The efficacy of ensifentrine was evaluated in two phase 3 trials (ENHANCE-1 and ENHANCE-2).⁹ Patients enrolled in the 2 randomized controlled trials (RCTs) were 40 to 80 years of age, with moderate to severe COPD, with a post-bronchodilator FEV₁ 30% to 70%, and a smoking history of 10 or more pack-

years.⁹ In ENHANCE-1, patients were a mean age of 65 years, with a mean postbronchodilator predicted FEV₁ of 52%, 57% were current smokers, and 25% of patients reported COPD exacerbations within 15 months prior to the study.⁹ Patients in ENHANCE-2 were a mean age of 65 years, with a mean postbronchodilator predicted FEV₁ of 51%, 55% were current smokers, and 21% of patients reported COPD exacerbations within the 15 months prior to the study.⁹ In both trials, patients could receive concurrent LAMA or LABA therapy with or without an ICS but were ineligible if receiving a LAMA/LABA or a LAMA/LABA/ICS.⁹

The primary endpoint in these trials was impact on bronchodilation from baseline to week 12 as assessed by the change FEV₁ area under the curve from 0 to 12 hours (AUC_{0-12h}).⁹ Compared with placebo, ensifentrine improved the least squares mean (LSM) change in FEV₁ AUC_{0-12h} from baseline to week 12 in both RCTs (moderate quality evidence).⁹ Study results are presented in **Table 1**.

Table 1. ENHANCE Trials: LSM Change in FEV₁ AUC_{0-12h}^{9,10}

Trial	Placebo (mL)	Ensifentrine (mL)	Difference (mL)
ENHANCE-1	-26	61	87 (95% CI 55 to 119) p<0.0001
ENHANCE-2	-46	48	94 (95% CI 65 to 124) p<0.0001

Abbreviations: CI = confidence interval; FEV₁ AUC_{0-12h} = forced expiratory volume area under the curve; LSM = least square mean change

Adverse reactions that occurred in people treated with ensifentrine included back pain, hypertension, urinary tract infection, and diarrhea.⁹ Treatment with ensifentrine is also associated with an increased risk of psychiatric adverse reactions.⁸ Before initiating treatment with ensifentrine, healthcare providers should carefully weigh the risk and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior, and re-evaluate the risks and benefits of continuing treatment if such events occur.⁸ The oral PDE-4 inhibitor, roflumilast also carries this warning in the prescribing information.⁷

Ensifentrine was not studied with some inhaler regimens that are currently recommended for treatment of COPD. Patients receiving concurrent LAMA/LABA inhaler, which is recommended as first-line therapy for patients with moderate COPD, and patients with triple therapy (LAMA/LABA/ICS) were excluded from enrollment. This may limit generalizability of the results from these trials.¹¹ Head-to-head clinical trials with ensifentrine and other COPD maintenance medications have not been conducted. Additional data is needed to assess the impact of ensifentrine on COPD exacerbations, hospitalizations, and quality of life. Ensifentrine is included in the 2025 GOLD update as add-on maintenance medication in COPD patients who continue to have dyspnea despite use of LABA/LAMA therapy.¹²

The authors noted that ensifentrine significantly improves lung function, (high-quality evidence), dyspnea (high-quality evidence) and health status (moderate-quality evidence).¹²

Dupilumab Expanded Indication in COPD

In September 2024, DUPIXENT (dupilumab), a targeted immune modulator (TIM), received an expanded FDA-approved indication as an add-on maintenance treatment for adults with inadequately controlled COPD.¹³ Dupilumab is already approved for use in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.¹³ The FDA based the approval on pooled data from 2 RCTs (BOREAS and NOTUS) conducted in adults with COPD and chronic bronchitis who were receiving triple inhaler therapy (LAMA/LABA/ICS).^{14,15} Trial enrollment required an exacerbation history of at least 2 moderate or 1 severe exacerbation(s) in the previous year despite receiving maintenance triple inhaler therapy (ICS/LABA/LAMA) and symptoms of chronic productive cough for at least 3 months in the past year.^{14,15}

In the BOREAS trial, 939 patients with COPD who had a blood eosinophil count $\geq$ 300 cells/ μ L and an elevated exacerbation risk were randomized to dupilumab 300 mg or placebo subcutaneously (SC) every 2 weeks.¹⁴ The mean number of moderate or severe COPD exacerbations for the enrolled population in the previous year was 2.3.¹⁴ The primary end point was the annualized rate of moderate or severe COPD exacerbations at 52 weeks.¹⁴ The annualized rate of moderate or severe exacerbations was 0.78 with dupilumab and 1.10 with placebo (rate ratio [RR], 0.70; 95% CI, 0.58 to 0.86; p<0.001).¹⁴ The prebronchodilator FEV₁ increased from baseline to week 12 by a LSM of 160 mL with dupilumab and 77 mL with placebo (LSM difference, 83 mL; 95% CI, 42 to 125; P<0.001).¹⁴ The MCID for this change is 120 mL.⁵ At week 52, the SGRQ score had improved by a LSM of -9.7 with dupilumab and -6.4 with placebo (LSM difference, -3.4; 95% CI, -5.5 to -1.3; P=0.002). This change was statistically significant, but did not meet the MCID of 4 points.

In the NOTUS trial, which enrolled a similar population, the mean number of moderate or severe COPD exacerbations in the previous year was 2.1.¹⁵ The annualized rate of moderate or severe exacerbations after 52 weeks was 0.86 with dupilumab and 1.30 with placebo (RR, 0.66; 95% CI, 0.54 to 0.82; p<0.001).¹⁵ The prebronchodilator FEV₁ increased from baseline to week 12 with dupilumab (LSM change, 139 mL) as compared with placebo (LSM change 57 mL), with a LSM difference at week 12 of 82 mL (95% CI 40 to 124; P<0.001) and at week 52 of 62 mL (95% CI 11 to 113; P=0.02).¹⁵ At week 52, the decrease from baseline in SGRQ

total score (indicating quality of life improvement) was -9.8 points in the dupilumab group and -6.4 points in the placebo group (LSM difference, -3.4 points; 95% CI, -5.8 to -0.9).¹⁵ This change was statistically significant but did not meet the MCID of 4 points.¹⁵

In both trials, the incidence of adverse events (AEs) was similar in between dupilumab and placebo and consistent with the established profile of dupilumab.^{14,15} Dupilumab has been added to the 2025 GOLD guidelines, as an add-on treatment in patients maintained on LABA/LAMA/ICS therapy who are still experiencing exacerbations with symptoms of chronic bronchitis.¹² Mepolizumab (NUCALA), another TIM, recently received FDA-approval in May 2025 as an add-on maintenance treatment in adults with poorly controlled COPD and an eosinophilic phenotype.

Oregon Health Plan Policies

The evidence for ensifentrine and dupilumab in treating COPD was presented to the Oregon Pharmacy and Therapeutic Committee at their December 2024 meeting. The committee approved recommendations to implement PA criteria for both therapies to verify appropriate place in therapy for patients enrolled in the FFS OHP (see **Figure 1**). Preferred ICS/LABA inhalers on the FFS Preferred Drug List (PDL) include budesonide/formoterol; fluticasone/salmeterol and mometasone/formoterol. Preferred LAMA/LABA inhalers include umeclidinium/vilanterol and tiotropium/olodaterol. Non-preferred LABA, LAMA/LABA, and LAMA/LABA/ICS inhalers require PA.

Figure 1. Oregon Health Plan Prior Authorization Criteria for Dupilumab and Ensifentrine

- Dupilumab: Restrict use to adults with inadequately controlled COPD on triple inhaler therapy (LABA/LAMA/ICS).
- Ensifentrine: Ensure patient is using guideline directed therapy prior to adding ensifentrine nebulizer to therapeutic regimen of LABA or LAMA inhaler or ICS.

Conclusion

COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic medication therapy. Adhering to guideline-directed therapeutic recommendations can reduce COPD symptoms, decrease the risk of frequent exacerbations and improve quality of life for people living with COPD.¹² Two new therapies, dupilumab and ensifentrine, were recently approved by the FDA to enhance maintenance

treatment of COPD. Comparative trials with other COPD maintenance medications have not been conducted with either agent. However, these medications provide additional treatment options for patients with frequent COPD exacerbations despite optimized inhaler therapy. Both medications are included as therapeutic options in the 2025 GOLD update.¹² Dupilumab is cited as an intervention that reduces the frequency of COPD exacerbations in patients maintained on triple inhaler therapy.¹² Ensifentrine is included as an option for add-on maintenance therapy in patients with COPD who continue to have dyspnea despite LABA/LAMA therapy.¹²

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New Drugs for the Treatment of Uncomplicated Urinary Tract Infections

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Urinary tract infections (UTI) are common, with at least one infection per year occurring in 10-20% of women, and less than 1% of men, in the United States (U.S.).^{1,2} Increasing rates of resistance to antibiotics used for the treatment of UTI has elevated the need for new therapies to eradicate bacteria associated with these infections. Recently, there have been 3 new Food and Drug Administration (FDA) approvals for antibiotics to treat uncomplicated urinary tract infections (uUTIs): gepotidacin, pivmecillinam and sulopenem/probenecid. This newsletter will focus on the evidence and place in therapy for these new treatment options.

Background

Urinary tract infections are designated as uncomplicated or complicated based on infection location. Per the newly released Infectious Diseases Society of America (IDSA) complicated UTI guidelines, uUTIs are confined to the bladder and occur in afebrile women or men.³ A complicated UTI is infection extending beyond the bladder, including pyelonephritis, febrile UTI, UTI causing bacteremia, catheter-associated UTI, and prostatitis.³ The European Association of Urology (EAU) has recommended new nomenclature for the definitions of UTI which are localized (i.e., cystitis without any signs of systemic infection in either sex) and systemic UTI (i.e., an infection with signs and symptoms of systemic infection with or without localized symptoms that may originate from any site in the urinary tract of either sex, including pyelonephritis and prostatitis).⁴

Patients presenting with uUTI are most often treated empirically. The most causative organism for uUTIs is *Escherichia coli* (*E. coli*), accounting for approximately 75%-95% of infections.¹ Additional bacteria associated with uUTI are *Proteus mirabilis* (*P. mirabilis*), *Klebsiella pneumoniae* (*K. pneumoniae*) and *Staphylococcus saprophyticus* (*S. saprophyticus*).¹ Resistant uropathogens are more commonly seen in women 50 years and older, patients with recurrent uUTI, and patients with diabetes.⁴ The most recent guidelines from the IDSA on uUTI, published in 2011, recommend treatment options for women based on resistance patterns and likely causative organisms (**Table 1**).¹ Patient allergies and adherence, medication availability and cost should also be considered when selecting an antibiotic.

Table 1. IDSA First-line Empiric Treatments for Uncomplicated UTI¹

Treatment	Dose	Duration
Nitrofurantoin (slow release)	100 mg twice daily	5 days
Trimethoprim-sulfamethoxazole (TMP/SMX)	160/800 mg twice daily	3 days
Fosfomycin	3 grams	Single dose
Pivmecillinam*	400 mg twice daily*	5 days

* Previously approved in Europe prior to recent U.S. approval

The 2025 EAU guidelines recommend that TMP/SMX only be used empirically if resistance rates in the area of use are <20% for *E. coli*.⁴ The FDA issued a 2016 Safety Announcement advising against the use of fluoroquinolones for uUTIs for those who have other treatment options, due to the serious adverse events such as tendon rupture, tendinitis, and central nervous system side effects, associated with their use.⁵ Guidance by the EAU also enacted stringent regulatory actions recommending against the use of fluoroquinolones.⁴ They recommend that fluoroquinolones only be used when it is inappropriate to use other antibiotics. Beta-lactam antibiotics (e.g., amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) may also be considered as an alternative for treatment, but *E. coli* resistance rates can be high, especially in recurrent uUTI.

Sulopenem/probenecid (Orlynvah®)

Sulopenem/probenecid is a recently approved combination tablet for uUTI caused by *E. coli*, *K. pneumoniae* or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.⁶ Sulopenem is a penem antibacterial, specifically a broad-spectrum thiopenem β -lactam antibiotic with efficacy against multi-drug resistant bacteria.⁶ Probenecid is added to increase sulopenem serum concentrations and extend its half-life. The dose is sulopenem 500 mg/probenecid 500 mg as one tablet twice daily for 5 days, with food if possible to minimize gastrointestinal (GI) upset.⁶

Sulopenem/probenecid is not indicated for treatment of complicated UTIs, for complicated intra-abdominal infections or as step-down treatment after intravenous (IV) antibacterial treatment for these conditions.⁶

One randomized controlled trial (RCT) was used for the approval of sulopenem/probenecid (n=1579).⁷ Study participants were randomized to receive sulopenem 500 mg /probenecid 500 mg given orally twice daily for 5 days or ciprofloxacin 250 mg orally twice daily for 3 days. Adult women, 18 years of age or older with a positive urinalysis and 2 or more symptoms of uUTI (e.g., urinary frequency, urgency, dysuria, or suprapubic pain) were included in the study.⁷ *E. coli* was the most common causative organism, occurring in approximately 85% of patients.⁷

The primary endpoint was overall response, which combined clinical (resolution of patient reported UTI symptoms and no new UTI symptoms) and microbiological response (reduction of all baseline uropathogens to less than 10³ CFU/mL in the urine) on day 12.⁷ The overall response was compared in 2 subsets by testing ciprofloxacin microbiological susceptible mMITT (mMITT-S) and microbiological non-susceptible MITT (mMITT-R) ciprofloxacin patient urine samples from the modified intent to treat (mITT) population. Superiority of sulopenem/probenecid to ciprofloxacin was based on the mMITT-R population and noninferiority was based on the comparison of sulopenem/probenecid to ciprofloxacin in the mMITT-S population.⁷

Results for the primary endpoint of clinical and microbiologic response demonstrated superiority of sulopenem/probenecid at 12 days compared to ciprofloxacin in the subset of patients in the mMITT-R group with an absolute difference (AR) of 26.6% (95% confidence interval [CI], 15.1 to 37.4; p-value not reported).⁷ Sulopenem/probenecid was not noninferior to ciprofloxacin in the mMITT-S subset; however, sulopenem/probenecid was noninferior to ciprofloxacin in the mMITT population overall.⁷ Authors attributed this result to a higher proportion of patients with post-treatment asymptomatic bacteriuria (ASB) in the sulopenem/probenecid group, and noted that this group did not have a higher rate of clinical relapse.

A recent double-blind, randomized, noninferiority trial compared sulopenem/probenecid to amoxicillin/clavulanate in adult women (n=2222) with uUTI.⁸ The primary end point was overall success, defined as combined clinical cure and microbiological cure at day 12. Sulopenem/probenecid overall success occurred in 60.9% of patients compared to 55.6% of patients treated with amoxicillin/clavulanate (mean difference [MD] 5.4%; 95% CI, -0.8 to 11.5; noninferiority criteria met).⁸

The most common adverse events associated with sulopenem/probenecid were diarrhea, nausea, vulvovaginal mycotic infections, headache and vomiting.⁶ Sulopenem/probenecid compared to amoxicillin/clavulanate was found to have more frequent, treatment-emergent, mild adverse events.⁸ Individuals with hypersensitivity, blood dyscrasias, or uric acid kidney stones, should not take

sulopenem/probenecid. Serious adverse reactions associated with sulopenem/probenecid are hypersensitivity reactions, which are associated with all β -lactam antibiotics.

Sulopenem/probenecid inhibits ornithine aminotransferase (OAT) 1/3 which can increase drug concentrations of medications that use this enzyme system for elimination.⁶ Use with ketorolac is contraindicated and use with ketoprofen is not recommended.⁶

Gepotidacin (Blujepa®)

Gepotidacin is a new antibiotic approved in March of 2025 for the treatment of uUTI infections in female adult patients and pediatric patients 12 years of age and older who weigh at least 40 kg with the following susceptible organisms: *E. coli*, *K. pneumoniae*, *C. freundii* complex, *S. saprophyticus*, and *E. faecalis*.⁹ Gepotidacin works by a different mechanism of action than other antibiotics. It is a triazaacenaphtheylene bacterial type II topoisomerase inhibitor, which blocks deoxyribonucleic acid (DNA) replication by the inhibition of DNA gyrase and topoisomerase IV.⁹ The dose of gepotidacin is two 750 mg (1500 mg) tablets twice daily for 5 days, taken after a meal.⁹ Gepotidacin should not be used in patients with complicated UTI.

The approval of gepotidacin was based on 2 similar methodologically designed studies to determine efficacy.¹⁰ Both studies were randomized, double-blind, double-dummy, phase 3, non-inferiority studies comparing gepotidacin 1500 mg twice daily for 5 days to nitrofurantoin 100 mg (slow release formulation) twice daily for 5 days (EAGLE-2 and EAGLE-3).¹⁰ Qualifying uropathogens were: gram-negative bacilli, (*S. saprophyticus* or *Enterococcus* species) at concentrations of $\geq 10^5$ CFU/mL.¹⁰ The average of age of participant was 52 years and 50 years in EAGLE-2 and EAGLE-3, respectively. The majority of patients in both studies had urine cultures positive for *E. coli*.¹⁰

The primary endpoint was therapeutic response, which combined clinical (e.g., symptom score of 0) and microbiological response (e.g., reduction of qualifying uropathogens to less than 10³ CFU/mL in the urine). Uropathogens had to be susceptible to nitrofurantoin to be included in the microbiological intention to treat (ITT) nitrofurantoin (NTF-S) population.¹⁰ Both studies were stopped early due to gepotidacin efficacy after interim analysis.

Gepotidacin was non-inferior to nitrofurantoin in both studies for those isolates that did not have resistance to nitrofurantoin. Gepotidacin achieved therapeutic success in 50.6% of gepotidacin patients compared to 47.0% of patients taking nitrofurantoin (treatment difference [TD] 4.3%; 95% CI, -3.6 to 12.1) in EAGLE-2.¹⁰ In EAGLE-3, gepotidacin was noninferior and superior to nitrofurantoin (TD 14.6%; 95% CI, 6.4 to 22.8;

p=0.003/ absolute risk reduction [ARR] 14.6/number needed to treat [NNT] 7) for the combined primary endpoint.¹⁰ In EAGLE-2 clinical success was the same between groups (65%) and microbiological success was greater in the gepotidacin group (67.9%) compared to nitrofurantoin (63.3%) in EAGLE-3.¹⁰

The most common adverse events associated with the use of gepotidacin are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting and vulvovaginal candidiasis.⁹ Gepotidacin should not be taken with drugs that inhibit CYP3A4 enzymes and in those with severe hepatic (Child-Pugh Class C) or renal (estimated glomerular filtration rate [eGFR] <30 ml/min) impairment due to the risk of increased concentrations of gepotidacin.⁹

Pivmecillinam (Pivya®)

Pivmecillinam was approved in April of 2024 by the FDA for uUTI.¹¹ Pivmecillinam is a penicillin antibacterial used for the treatment of uUTI in female patients 18 years old and older caused by susceptible isolates of *E. coli*, *P. mirabilis* and *S. saprophyticus*.¹¹ Pivmecillinam is given as one 185 mg tablet by mouth 3 times a day for 3-7 days as clinically indicated. Pivmecillinam is not approved for complicated UTI. Pivmecillinam has been approved in Europe for over 40 years.

Pivmecillinam is a pro-drug of mecillinam that targets penicillin-binding protein 2 (PBP2).¹¹ This bacterial enzyme is not routinely targeted by other β -lactam antibiotics and makes it effective against pathogens like *E. coli*.

Pivmecillinam was studied in 3 clinical trials for FDA approval. Only one of these trials was a comparative efficacy trial to an antibiotic, cephalexin, used for uUTI.¹² The other trials were a placebo-controlled trial and a trial comparing pivmecillinam to ibuprofen.^{12,13}

Pivmecillinam 185 mg three times daily for 3 days was compared to cephalexin 250 mg four times daily for 7 days in a multi-center, double-blind RCT (n=440) in the U.S.¹² Women 18 years and with uUTI were included. The composite endpoint was clinical (i.e., no symptoms that persisted during treatment or post treatment) and microbiological cure. Microbiological cure was a negative urine culture on day 10 for presenting pathogen.¹² Microbiological cure and clinical cure was not statistically significantly different between pivmecillinam and cephalexin (**Table 2**).¹² For the combined endpoint of clinical and microbiological cure, 72% of those treated with pivmecillinam compared to 76% of patients treated with cephalexin achieved that outcome (TD -4%; 95% CI, -16 to 7; p>0.05).¹²

In a phase 3 study, pivmecillinam 185 mg three times daily was compared to ibuprofen 600 mg daily three times daily.¹³ Both regimens were given for 3 days. The trial was a double-

blind, double dummy, noninferiority trial. Patients were asked to record symptoms daily, including if they felt cured, in a diary. The main outcome was proportion of patients who felt cured by day 4, as recorded in their diary.¹³ A key secondary outcome was the proportion of patients with a positive second urine culture at 14 days for primary pathogen.

Pivmecillinam was found to be associated with a higher number of patients who felt cured by day 4 of treatment compared to those randomized to ibuprofen. Ibuprofen was chosen as a comparator to see if symptomatic uUTI treatment could reduce antibiotic use since uUTIs are often self-limiting. The difference was not large enough to consider pivmecillinam to be more effective compared to ibuprofen (risk difference [RD] 35%; 95% CI, 27% to 43%; noninferiority not met) (**Table 2**).¹³ There were fewer patients in the pivmecillinam group with a positive bacterial culture at 14 days compared to the ibuprofen group (RD -16%; 95% CI, -26% to -7%; p<0.001; ARR] 18%/NNT 6).¹³

In a double-blind, phase 3 RCT comparing 3 different doses of pivmecillinam to placebo, pivmecillinam was more effective for all doses. Pivmecillinam was given as 200 mg three times daily for 7 days, 200 mg twice daily for 7 days or 400 mg twice a day for 3 days. The trial was a double dummy design, so all patients received identical-appearing tablets. For the composite response rate of clinical and microbiological cure, the combined doses of pivmecillinam were more effective than placebo (ARR 52%/NNT 2) (**Table 2**)¹¹.

Table 2. Pivmecillinam for the Treatment of uUTI		
Study	Outcome	Result
Pivmecillinam vs. Placebo ¹¹	Composite Response Rate (clinical and microbiological cure)	Combined pivmecillinam groups: 85 (62%) Placebo: 14 (10%) TD 52% (95% CI, 41 to 62)
Pivmecillinam vs. Cephalexin ¹²	Clinical cure	Pivmecillinam: 102 (95.3%) Cephalexin: 102 (93.6%) P=0.58
	Microbiological cure	Pivmecillinam: 96 (89.7) % Cephalexin: 89 (81.7%) P=0.09
Pivmecillinam vs. Ibuprofen ¹³	Patient reported symptoms of being cured	Pivmecillinam: 131 (73.6%) Ibuprofen: 70 (38.7%) Noninferiority criteria not met
Abbreviations: CI = confidence interval, TD = treatment difference		

Oregon Health Plan Fee-for-service Policy

Prior authorizations are required for all 3 new antibiotics indicated for uncomplicated urinary tract infections:

- Gepotidacin (Blujepa®)
- Pivmecillinam (Pivya®)
- Sulopenem/probenecid (Orlymvah®)

Conclusions

Appropriate antibiotic use for the treatment of uUTI is important for symptom resolution and to minimize development of resistant organisms. New medications indicated for uUTI may be considered for women who require second line treatment options due to intolerance to first line therapies or antibiotic resistance. Evidence for all 3 new drugs is limited by small trials of short duration that show little or small magnitude of benefit over existing therapies, and they will likely be more expensive than generic first-line treatment options which cost approximately \$10 per treatment course.

Peer Reviewer: Sujeet Govindan, M.D., Assistant Professor in Infectious Disease, OHSU School of Medicine and Holly Villamagna, M.D. Assistant Professor, Division of Infectious Diseases, Oregon Health & Science University

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2025 American College of Cardiology/American Heart Association Joint Committee Clinical Practice Guideline Update

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group

Hypertension is the most common cause of cardiovascular disease (CVD).¹ About 46.7% of the United States population has a diagnosis of, or is receiving therapy for, hypertension. Even with many antihypertensive treatment options, many people are not obtaining goal blood pressure (BP) levels. High blood pressure, defined as levels at or above 130/80 mm Hg, are associated with an increased risk of CVD, kidney disease, coronary heart disease (CHD), heart failure (HF), aortic and peripheral vascular disease, ischemic and hemorrhagic stroke, dementia, and cognitive impairment.¹ Early identification and treatment of hypertension is important to decrease risk of irreversible vascular damage and prevent further damage after treatment is initiated.

New recommendations from the American College of Cardiology (ACC)/American Heart Association (AHA) Joint Committee on Clinical Practice Guidelines replaces recommendations from the previous 2017 publication on the prevention, detection, evaluation and management of high BP in adult patients.¹ Evidence from February 2015 to June 2024 was included. Nineteen recommendations were new or revised and 10 take home messages were emphasized. There were new or updated recommendations for treatment goals and drug therapy in people with diabetes, elevated CVD risk, chronic kidney disease (CKD), mild cognitive impairment and dementia, and pregnancy. This newsletter will focus on guideline recommendations related to drug therapies, including when to initiate therapy and goal BP levels.

Grading of Recommendations

Recommendations provided by the ACC/AHA were given a Class of Recommendation (COR) and Level of Evidence (LOE) grading (**Table 1**).¹

Table 1. Class of Recommendation and Level of Evidence Designation from the ACC/AHA¹

Class of Recommendation	
Class 1 (Strong)	Benefit >>> Risk
Class 2a (Moderate)	Benefit >> Risk
Class 2b (Weak)	Benefit > Risk
Class 3: No Benefit (Moderate)	Benefit = Risk
Class 3: Harm (Strong)	Risk > Benefit
Level (Quality) of Evidence	
Level A	High quality evidence from more than 1 RCT or meta-analyses of high-quality RCTs

Level B-R (Randomized)	Moderate quality evidence from RCTs
Level B-NR (Nonrandomized)	Moderate quality evidence from nonrandomized controlled trials
Level C-LD (Limited Data)	Observational or registry data
Level C-EO (Expert Opinion)	Consensus data
Abbreviation: RCT = randomized controlled trial	

Risk Estimation

The ACC/AHA recommends the PREVENT (Predicting Risk of CVD EVENTS) equation for estimation of 10-year risk for total CVD for adults with hypertension without clinical CVD.¹ PREVENT estimates risk for total CVD (myocardial infarction [MI], stroke, and heart failure [HF]) and recommends that antihypertensives be initiated in patients that have a 10-year CVD risk at or above 7.5%. The risk calculator is available online at: <https://professional.heart.org/en/guidelines-and-statements/prevent-risk-calculator/prevent-calculator>.

Lifestyle Modifications for Blood Pressure

Lifestyle modifications are recommended to help lower blood pressure and reduce stress. Systolic blood pressure can decrease from 5 to 10 mm Hg, depending on the lifestyle modification. Interventions that are suggested are:

- ❖ Weight loss
- ❖ Heart healthy diet (DASH diet)
- ❖ Reduced sodium intake
- ❖ Use of salt substitute
- ❖ Enhanced intake of potassium
- ❖ Reduced alcohol intake
- ❖ Exercise
- ❖ Meditation
- ❖ Breathing control

Thresholds for Initiating Antihypertensive Therapy

BP treatment thresholds to guide medication initiation are outlined in **Table 2**.¹ For all patients and all stages of hypertension, lifestyle modifications to lower blood pressure is recommended.

Table 2. Recommendations for Medication Treatment based on Blood Pressure Thresholds¹

BP Level	Population	Recommendation
Normal BP (<120/80 mm Hg)		Reassess in 1 year
Elevated BP (120-129/<80 mm Hg)		Reassess in 3-6 months
Stage 1 HTN (130-39/80-89 mm Hg)	DM, CKD, or 10-year CVD risk $\geq 7.5\%^*$	Antihypertensive medication
	No DM or CKD, and 10-year CVD risk $< 7.5\%^*$	Reassess in 3-6 months
Stage 2 HTN ($\geq 140/ \geq 90$ mm Hg)	Antihypertensive medication	
Key: * Risk of CVD based on PREVENT risk $\geq 7.5\%$ Abbreviations: BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes; HTN = hypertension; PREVENT = Predicting Risk of CVD EVENTS		

Strong recommendations for use of antihypertensives are based on high-quality supporting evidence for the reduction of CVD events and total mortality.¹ The following recommendations are designated as COR Level 1 and LOE A:

- In adults, medications should be initiated when average systolic blood pressure (SBP) is ≥ 140 mm Hg and/or the diastolic blood pressure (DBP) is ≥ 90 mm Hg.
- In adults with an average SBP ≥ 130 mm Hg, initiation of antihypertensive medications is recommended for people with:
 - o clinical CVD
 - o diabetes
 - o chronic kidney disease (CKD)
 - o increased short-term risk of CVD (i.e., risk of 10-year CVD $\geq 7.5\%$ based on PREVENT) but without clinical CVD.

Medication to lower blood pressure is recommended in adults with DBP ≥ 80 mm Hg based on COR 1 and LOE C-LD for people with clinical CVD, diabetes, CKD, or with 10-year CVD risk $\geq 7.5\%$ based on PREVENT.¹

In adult patients with type 2 diabetes (T2D) and hypertension, therapy should be initiated at SBP ≥ 130 mm Hg with a target of < 130 mm Hg and less than 120 mm Hg if possible (COR 1; LOE A).¹ Those with T2D and hypertension and a DBP ≥ 80 mm Hg should receive treatment with a goal of < 80 mm Hg (COR 1; LOE C-LD).¹ All first-line therapies are an effective choice for patients that also have T2D. In those with hypertension, T2D and CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m² or albuminuria ≥ 30 mg/g), an ACEi or ARB should be considered to prevent progression of diabetes related kidney disease (COR 1; LOE A).¹

Antihypertensive Therapy Selection

Initial antihypertensive therapies should be based on patient comorbidities, such as presence of CAD, HF, stroke, diabetes and/or CKD. First-line antihypertensive classes recommended are: thiazide-type diuretics, long-acting dihydropyridine calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARBs).¹ All first-line treatments have high-quality evidence for BP lowering, CVD prevention and tolerability.¹ Preferred medications for fee-for-service (FFS) members are outlined in **Figure 1**.²

In adult patients with stage 2 hypertension (SBP > 140 mm Hg or DBP > 90 mm Hg), starting treatment with 2 first-line therapies from different classes is recommended to improve BP (COR 1; LOE B-R).¹ Therapies combined in a single-pill is suggested to improve adherence and observational data suggests reduced CV events and all-cause deaths when compared to an equivalent multiple-pill combination. Current FDA approved combinations are: ACEi or ARB + thiazide-type diuretic, ACEi or ARB + CCB, potassium-sparing diuretic + thiazide-type diuretic, mineralocorticoid receptor antagonist (MRA) + thiazide-type diuretic, and ARB + CCB + thiazide-type diuretic.¹ Antihypertensive single pill combinations that are preferred for FFS members are outlined in **Figure 2**.²

Specific Recommendations Pertaining to Medication Use or Avoidance

Simultaneous use of an ACEi, ARB and/or renin inhibitor in combination is not recommended due to harm (i.e., CVD, kidney disease and hyperkalemia).¹ Non-dihydropyridine CCBs should not be used in patients with HF with reduced ejection fraction (HFrEF). Beta-blockers should not be used first-line unless the patient has coronary heart disease (CHD) or HF. Non-selective beta blockers should be avoided in patients with reactive airway disease. Aliskiren should not be used in combination with ACEi or ARB. Central alpha-2-agonists and other centrally acting antihypertensives are not recommended due to adverse central nervous system (CNS) effects.

In patients with HF or moderate-to-severe CKD loop diuretics are the preferred diuretic choice. Metoprolol succinate and bisoprolol are preferred in patients with HFrEF. The combined alpha and beta blocker, carvedilol, is preferred in patients with HFrEF. Consider using alpha-1 blockers as second-line agents in patients with symptomatic benign prostatic hypertrophy. Aprocritentan is a dual endothelin receptor antagonist that should be reserved for add-on therapy when patients have uncontrolled blood pressure on other therapies due to risk of mild-to-moderate fluid retention with aprocritentan use.

Figure 1. Recommended First-Line Antihypertensives that are on the Preferred Drug List for FFS Members²

Figure 2. Combination Antihypertensive that are on the Preferred Drug List for FFS Members²

Table 3. ACC/AHA Goal Blood Pressure Recommendations for Adults with Hypertension¹

Indication	Recommendation	Evidence
HTN	SBP < 130 mm Hg DBP < 80 mm Hg	COR: 2b LOE: B-NR
HTN and increased risk of CVD	SBP < 130 mm Hg	COR: 1 LOE: A
	DBP < 80 mm Hg	COR: 1 LOEL B-R
HTN and T2D	<130 mm Hg SBP	COR: 1 LOE: A
	< 80 mm Hg DBP	COR 1 LOE: C-LD
HTN and Prevention of HF	SBP < 130 mm HG DPB < 80 mm Hg	COR: 1 LOE: B-R
HTN and CKD	SBP < 130 mm Hg	COR: 1 LOE: A
HTN and secondary stroke prevention	SBP < 130 mm Hg DBP < 80 mm Hg	COR: 1 LOE: B-R
HTN and mild cognitive impairment	SBP < 130 mm Hg	COR: 1 LOE: A
HTN and pregnancy	SBP < 140 mm Hg DBP < 90 mm Hg	COR: 1 LOE: B-R

Conclusions

There is conclusive evidence that obtainment of BP levels to target goals helps to reduce risk of CVD and events in those with established disease. There are many proven antihypertensives available to assist patients in meeting their blood pressure goals. Patients may require multiple antihypertensives and regular reassessment to obtain target blood pressures. The use of first-line therapies should be maximized to reduce the risk of CVD and mortality.

Peer Reviewers: John MacKay, PharmD, BCPS, Clinical Pharmacist, Advanced Heart Failure and Heart Transplant, Providence Medical Group

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Hypertension and Pregnancy

Women with hypertension that are pregnant or planning on becoming pregnant should be on antihypertensives to minimize fetal risk. Labetalol and extended-release nifedipine are recommended as options (COR 1; LOE A).¹ Atenolol, ACEi, ARB, direct renin-inhibitors, nitroprusside, or MRA should be avoided as they may cause fetal harm.¹ Higher BP goals are recommended to prevent fetal risk if BP is too low (**Table 3**).

Monitoring and Follow-up

In patients that have normal blood pressure measurements, yearly reassessment is recommended.¹ Patients with elevated blood pressure or Stage 1 hypertension without comorbidities or CVD risk should be seen for follow-up in 3-6 months. BP should reassessed 1 month after initiating antihypertensive medication and in 3-6 months if goal BP are met.¹ For most patients except people who are pregnant, the recommended goal blood pressure is < 130/80 mm Hg (**Table 3**).¹



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Drug Class Update: Antidepressants

Date of Review: February 2026

Date of Last Review: June 2024 (antidepressants)

June 2025 (esketamine)

January 2019 (fibromyalgia)

Dates of Literature Search: 04/01/2024 - 11/24/2025

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this update is to evaluate new literature on antidepressants since the last review and to develop evidence-based utilization management for drugs to treat current unfunded conditions (such as fibromyalgia). New evidence for generalized anxiety disorder (GAD), chronic pain, fibromyalgia and suicide prevention will be included as antidepressants, and related therapies, are used for these indications.

Plain Language Summary:

- This review looked at new research on medicines used to treat depression and other conditions. There are five main classes of antidepressants. They are called selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants.
- Antidepressants are used to help with anxiety, chronic pain, insomnia, migraine headache, fibromyalgia, bipolar disorder and obsessive-compulsive disorder (OCD).
- SNRIs may help with low back pain and TCAs help people stay active when they have low back pain.
- Some antidepressants, including SNRIs, SSRIs and vilazodone, can help improve symptoms of anxiety.
- SSRIs reduce symptoms of OCD.
- Two guidelines recommend amitriptyline to help prevent episodic migraine headache.
- One guideline recommends the combination of fluoxetine and olanzapine to treat bipolar disorder.
- One guideline recommends duloxetine and amitriptyline as treatment options to reduce pain caused by fibromyalgia.
- All antidepressants have side effects such as dry mouth, tiredness, and dizziness. Each person can respond differently to an antidepressant.
- Providers can prescribe any antidepressant they believe is best for the patient. Some antidepressants require approval, called prior authorization, due to safety concerns. The Drug Use Research and Management group does not recommend any policy changes based on this review.

Research Questions:

1. Is there new comparative evidence related to efficacy of antidepressants for important outcomes (e.g., symptom reduction and remission rates)?
2. Is there new comparative evidence for harms for antidepressants when used to treat depression?
3. Are there specific populations based on demographic characteristics, such as age, race, ethnicity, pregnancy status, or people with certain comorbidities, for which certain antidepressants are better tolerated or more effective than other antidepressants in improving symptoms and remission of depression?
4. What is the comparative evidence for efficacy and harms for antidepressants when used to treat conditions other than depression (e.g., fibromyalgia, chronic pain, and anxiety)?

Conclusions:

- This review identified three high-quality systematic reviews, six high-quality clinical practice guidelines, one randomized controlled trial (RCT), and five new safety alerts issued by the U.S. Food and Drug Administration (FDA).
- One systematic review found moderate quality evidence that serotonin norepinephrine reuptake inhibitors (SNRIs) may have a small effect at reducing low back pain intensity but not disability.¹ There is low quality evidence that they are associated with adverse events in this population. There are well documented adverse events with antidepressants when used for other indications. Tricyclic antidepressants (TCAs) may reduce disability related to low back pain but have no effect on intensity of pain based on moderate quality evidence.¹ The evidence for the efficacy of antidepressants in spine-related leg pain is unclear.¹
- A review by the Agency for Healthcare Research and Quality (AHRQ) found that treatment with SSRIs are more effective than placebo for reduction in obsessive compulsive disorder (OCD) symptoms and global severity outcomes based on high quality evidence.²
- An updated guideline from the National Institute of Health and Care Excellence (NICE) recommends amitriptyline as an option for migraine prophylaxis.³
- American College of Physicians (ACP) recommends antidepressants for the prevention of episodic migraine headaches.⁴ Venlafaxine or amitriptyline received a conditional recommendation supported by low-quality evidence.⁴
- NICE recommends fluoxetine, in combination with olanzapine, as an option to manage bipolar depression in adults.⁵
- The Scottish Intercollegiate Guidelines Network (SIGN) recommends amitriptyline and duloxetine for patients with fibromyalgia (high quality evidence; Grade A recommendation).⁶ Milnacipran has similar evidence of effectiveness for the treatment of fibromyalgia but was not included in the guideline because it is not available in the UK.⁶
- The Oregon Health Authority (OHA) Mental Health Clinical Advisory Group (MHCAG) recommends initial treatment of major depressive disorder (MDD) with a selective serotonin reuptake inhibitors (SSRI), SNRI, bupropion or mirtazapine.⁷ For treatment resistant depression (TRD), augmentation with a non-SSRI/SNRI antidepressant, bupropion sustained release (SR) or extended release (ER) and mirtazapine are recommended.⁷ Esketamine nasal spray was also recommended for TRD as augmentation therapy.⁷
- The MHCAG recommends treatment with escitalopram, sertraline, duloxetine or venlafaxine ER for GAD.⁸ Buspirone is recommended as second-line adjunct treatment option.⁸
- For the treatment of chronic insomnia in adults, specific antidepressants have demonstrated efficacy. The MHCAG recommends doxepin and trazodone as antidepressants as having evidence for use.⁹
- Antidepressants are used in the treatment of post-traumatic stress disorder (PTSD). Paroxetine, sertraline and venlafaxine ER have moderate quality evidence to support their use in PTSD and are recommended by MHCAG.¹⁰
- The MHCAG recommended removal of the 34-day limit on non-controlled mental health drugs and controlled IV-V mental health drugs in March of 2025.¹¹ This change will allow pharmacies to bill for a 100-day supply of preferred medications as currently authorized for other chronic medications.

- There is insufficient evidence on one specific antidepressant over another for specific subpopulations.

Recommendations:

- No preferred drug list (PDL) changes are recommended based on a review of the evidence.
- Update PA criteria for allow for coverage of evidence supported indications for milnacipran.
- Add at least one formulation of lithium and buspirone to the PDL to facilitate access to a 100-day supply.
- Evaluate drug costs in the executive session.

Summary of Prior Reviews and Current Policy:

- Antidepressants are designated as preferred or part of the voluntary PDL. Specific antidepressants have criteria to promote safe and medically appropriate use. Because there is limited data to demonstrate clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants, previous recommendations from the Pharmacy and Therapeutics (P&T) Committee are to base antidepressant treatment selection on individual patient preference, past response to antidepressants, risk for specific harms, and cost.
- Beginning in October 2025, the Oregon Health Authority fee-for-service program began allowing enrolled pharmacies to bill preferred mental health drugs for up to a 100-day supply.
- The antidepressant class was last reviewed by the Committee in June 2024. Gepirone was maintained as voluntary non-preferred on the mental health PDL and the TCA PA criteria were updated as recommended by the MHCAG.
- Tazodone, brexanolone (no longer available) and olanzapine/fluoxetine were assigned voluntary non-preferred status after cost review in executive session.
- Esketamine was last reviewed in June 2025 and the PA criteria were updated to allow for esketamine monotherapy for people with TRD.

Background:

Antidepressant medications are categorized based on mechanism of action and chemical structure. They are classified as first-generation (TCAs and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs and SNRIs, and newer antidepressants). They are used for a wide variety of psychiatric and medical conditions including depression, PTSD, bipolar disorder, obsessive compulsive disorder, and anxiety disorders. Specific antidepressants have FDA-approved indications for other conditions including fibromyalgia (which is currently not a funded diagnosis on the Oregon Health Plan), diabetic peripheral neuropathy, chronic pain, post-partum depression (PPD), PMDD, migraine, bulimia, and smoking cessation.¹² Evidence supported indications and recommended therapies are presented in **Table 1**.

Table 1. Recommendations for Antidepressant Use

Antidepressant Indication	Antidepressants with Evidence for Use	Place in Therapy
Bipolar	• Olanzapine-fluoxetine • Adding SSRI or bupropion to another mood stabilizer medication	- Lamotrigine, lithium, and quetiapine are recommended first line¹³ - Avoid antidepressant monotherapy¹³
Bulimia	• Fluoxetine • Sertraline • Escitalopram	- Fluoxetine is recommended first line¹⁴

	• Fluvoxamine • Desipramine • Nortriptyline • Trazodone	- Paroxetine and citalopram are not recommended due to weight gain or cardiac effects¹⁴ - Bupropion should be avoided due to risk of seizures in this population¹⁴
Chronic insomnia disorder	• Doxepin • Trazodone	- Non-pharmacologic therapies (i.e., sleep hygiene and psychotherapy) are recommended first line⁹ - Short term (up to 4 weeks) is recommended if an antidepressant is used⁹ - Mirtazapine and amitriptyline lack evidence or are associated with adverse events and are not recommended⁹ - Doxepin, trazodone, lemborexant, and suvorexant recommended for sleep maintenance⁹ - Zolpidem, eszopiclone, temazepam recommended for sleep onset and maintenance⁹ - Triazolam recommended for sleep onset⁹
Chronic Pain	• Duloxetine	- Milnacipran may reduce pain but supported by less evidence⁶ - Other antidepressants are supported by low quality evidence for effectiveness⁶
Fibromyalgia	• Duloxetine • Milnacipran • Amitriptyline • Pregabalin • Cyclobenzaprine	- Duloxetine, amitriptyline, milnacipran, cyclobenzaprine, pregabalin and gabapentin are recommended first-line drug therapy options¹⁵ - Non-pharmacologic therapy should be tried before starting medications¹⁵
Generalized Anxiety Disorder	• Escitalopram • Sertraline • Duloxetine • Venlafaxine ER • Imipramine • Bupropion ER	- escitalopram, sertraline, duloxetine or venlafaxine ER are recommended as first-line⁸ - imipramine has evidence of efficacy but is associated with side effects and toxicity⁸

		- Antidepressants recommended over buspirone due to slow onset and frequent daily dosing⁸
Major depressive disorder	• All except for milnacipran	- Initial treatment with SSRI, SNRI, bupropion or mirtazapine⁷ - Zuranolone is the only antidepressant approved for PPD⁷ - Bupropion SR or ER, mirtazapine and esketamine are recommended as antidepressant augmentation treatment options for those with TRD (failure of 2 or more antidepressants given at therapeutic doses⁷
Migraine	• Amitriptyline • Venlafaxine • Fluoxetine	- Amitriptyline and venlafaxine have the most evidence for use for migraine prevention⁴
Obsessive compulsive disorder	• Fluoxetine • Fluvoxamine • Paroxetine • Sertraline • clomipramine	- SSRIs are recommended first line.¹⁶ - Psychotherapy is also recommended
Neuropathic pain	• Duloxetine • Venlafaxine • Amitriptyline • Nortriptyline • Desipramine	- Duloxetine, venlafaxine and amitriptyline are recommended as the first line antidepressant treatment choices¹⁷
Post partum depression	• Sertraline • Fluoxetine • Venlafaxine • Zuranolone	- Psychotherapy is also recommended¹⁸
Post-traumatic Stress Disorder (PTSD)	• Paroxetine • Sertraline • Venlafaxine XR	- Psychotherapy is recommended first line - Paroxetine, sertraline, and venlafaxine XR recommended for the treatment of PTSD¹⁰
Premenstrual Dysphoric Disorder	• Sertraline • Citalopram • Escitalopram	- Paroxetine is associated with weight gain and not recommended¹⁹

	• Fluoxetine • Venlafaxine	
Smoking Cessation	• Bupropion SR	- Treatment duration of 3 month is usually recommended ²⁰

Abbreviations: PPD – post-partum depression; SNRI -serotonin norepinephrine reuptake inhibitor; SSRI – selective serotonin reuptake inhibitor; TRD – treatment resistant depression; XR – extended-release.

All antidepressants have an FDA boxed warning for suicide risk in young adults and can be associated with a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.²¹

Goals of treatment for depression typically include symptom and function improvement, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients living with depression. Scales vary depending on the condition. Some of the most commonly used rating scales include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.¹² The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52) with scores of 10-13 indicating mild depression, 14-17 indicating mild to moderate depression and 17 and greater indicating moderate to severe depression.¹² The FDA has stated that this tool is valuable in the study of depressive symptoms but may be associated with a higher representation of evaluation of somatic symptoms (e.g., insomnia and somatic anxiety) compared to other tools.²² Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes, and response to therapy is typically defined as a 50% improvement in symptom score from baseline.¹² A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and HAM-D scores of 3 to 7 points may be clinically significant.¹²

In patients with GAD the Hamilton Anxiety Rating Scale (HAM-A) is used to assess efficacy. The HAM-A is a 14 item scale which rates symptoms on a 5-point scale from 0 to 4 with total scores ranging from 0-56.²³ Anxiety rating are minimal (0-7), mild (8-14), mild to moderate (15-24), moderate to severe (25-30), and severe to very severe (31-56).²³

In Oregon, mental health drug classes, including antidepressants, are carved out from the coordinated care organizations (CCOs) and paid for by FFS. Non-preferred products do not automatically require prior authorization, but safety criteria are in place for esketamine, zuranolone and TCAs in children. antidepressant medication claims for OHP fee-for-service (FFS) members. There were over 400,000 antidepressant claims in quarter 2 of 2025. Milnacipran requires prior authorization to ensure that it is prescribed for an OHP-funded diagnosis in adults with evidence supporting its use in that condition.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are

critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane – Antidepressants for Low Back Pain and Spine-related Leg Pain

A 2024 Cochrane review evaluated treatments used for low back pain and spine-related leg pain in participants that were 18 years and older.¹ Type of pain included non-specific low back pain or spine-related pain of any duration. Patients with low back pain because of spinal fracture, inflammatory disease, aortic dissection, malignancy or infection were excluded. The main outcomes studied were pain intensity and disability, measured during short-term follow-up between 4 weeks to 14 weeks, and adverse events.¹ Twenty-six randomized trials, all of which were placebo-controlled, were included. Studies of non-specific low back pain accounted for 18 studies and 7 studies evaluated spine-related leg pain.¹ One study included patients with either condition. The mean duration of pain was 18 months to 20 years.¹ Participant's ages ranged from 27-59 years. Antidepressants studied were SNRIs (8 studies of duloxetine and milnacipran), SSRIs (2 studies of paroxetine), TCAs (14 studies of amitriptyline, clomipramine, desipramine, imipramine and nortriptyline), and 2 studies of other antidepressants (i.e., bupropion and trazodone).¹

The results are presented in **Table 2** for studies evaluating non-specific low back pain and **Table 3** for studies of spine-related leg pain. Other antidepressants were not studied for the outcome of disability in non-specific low back pain. There were no studies of SSRIs or other antidepressants that studied spine-related leg pain. One of the main limitations was high attrition bias in 69% of the studies.¹ This may bias the results by creating differences in the participant groups leading to underestimation or overestimation of antidepressant effects for low back pain and spine-related pain.

Table 2. Non-Specific Low Back Pain¹

Outcome	Result	Certainty of Evidence	Interpretation
SNRIs - duloxetine and milnacipran (4 studies)			
Pain Intensity†	MD -5.25; 95% CI, -7.17 to -3.34	Moderate	Likely a small benefit
Disability‡	MD -0.91; 95% CI, -1.30 to -0.51	Moderate	Likely a trivial effect
SSRIs – paroxetine (3 studies for pain; 1 for disability)			
Pain Intensity†	MD 1.20; 95% CI, -4.90 to 7.30	Low	Little to no effect
Disability*	MD -2.20; 95% CI, -8.11 to 3.71	Low	Little to no effect
TCAs – amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline (4 studies)			
Pain Intensity	MD -2.00; 95% CI, -7.25 to 3.24	Moderate	Little to no effect
Disability‡	MD -1.76; 95% CI, -2.70 to -0.82	Moderate	Small effect
Other Antidepressants – bupropion (1 study)			
Pain intensity	MD -5.40; 95% CI, -23.08 to 12.28	Very low	Little to no effect

Key: *Disability scale of 0-100 scale; † Pain scale of 0-100; ‡ Disability scale of 0-24.

Abbreviations: CI = confidence interval; MD = mean difference; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Table 3. Spine-Related Leg Pain¹

Outcome	Result	Certainty of Evidence	Interpretation
SNRI - Milnacipran (1 study)			
Pain Intensity	MD -46.10; 95% CI, -89.29 to -2.91	Very low	Evidence is uncertain
Disability*	MD -4.40; 95% CI, -20.25 to 11.45	Very low	Evidence is uncertain
TCA – amitriptyline (1 study)			
Pain Intensity†	MD -23.00; 95% CI, -32.12 to -13.88	Low	May have a large effect
Disability*	MD -13.00; 95% CI, -19.42 to -6.58	Moderate	May have a moderate effect

Key: *Disability scale of 0-100; † Pain scale of 0-100.

Abbreviations: CI = confidence interval; MD = mean difference; SNRIs = serotonin norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

When evaluating harms data, all the evidence was considered low or very low quality except for the SNRIs. There is limited evidence for antidepressant use for these indications, which influenced the evidence rating. SNRIs probably increase the risk of adverse events (relative risk [RR] 1.17; 95% CI, 1.07 to 1.27) with short-term use over 4 to 14 weeks based on moderate quality evidence.¹ Adverse events for TCAs and SSRIs were not statistically different than placebo in short term RCTs, lasting 4-14 weeks, but the data is unclear and estimates are imprecise.¹ There were no data on the adverse events of other antidepressants.

Cochrane – Antidepressants versus Placebo for Generalized Anxiety Disorder

A 2025 Cochrane review evaluated the safety and efficacy of antidepressants for treatment of GAD in adults.²⁴ Thirty-seven placebo-controlled RCTs (n=12,226) were included. All participants had a diagnosis of moderate to severe GAD. Settings included inpatient and outpatient populations with treatment lasting from four to 28 weeks.²⁴ Drugs studied were duloxetine, escitalopram, imipramine, paroxetine, sertraline, venlafaxine, vilazodone and vortioxetine.²⁴ Participants with severe medical comorbidities were excluded. The main outcomes studied were change in HAM-A rating and discontinuations due to adverse effect or lack of efficacy.

Results are presented in **Table 4**. There were four categories of comparison: all antidepressants, SSRIs, SNRIs and ‘other’ antidepressants (e.g., vilazodone).²⁴ Among the different classes of antidepressants, all medication classes are more effective than placebo in a reduction of at least 50% on the HAM-A (i.e., treatment response). For the comparisons of all antidepressants to placebo the treatment response was statistically and clinically significant with a reported number needed-to-treat [NNT] of 7.²⁴

Table 4. Antidepressants Compared to Placebo²⁴

Outcome	Result	Certainty of Evidence	Interpretation
All Antidepressants			
Treatment Response* (follow-up 6-24 weeks)	RR 1.41; 95% CI, 1.29 to 1.55	High	Antidepressants improved symptoms more than placebo

Total number of dropouts (follow-up 4-28 weeks)	RR 1.03 ; 95% CI, 0.93 to 1.14	High	There was no difference between groups
Dropouts due to lack of efficacy (follow-up 6-28 weeks)	RR 0.41; 95% CI 0.33 to 0.50	High	Treatment with an antidepressant decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 6-28 weeks)	RR 2.18; 95% CI, 1.81 to 2.61	High	Antidepressants were more likely to cause discontinuations due to adverse events compared to placebo
SSRIs			
Treatment Response* (follow-up 8-12 weeks)	RR 1.51; 95% CI, 1.20 to 1.90	High	Treatment with antidepressants improved symptoms more than placebo
Total number of dropouts (follow-up of 4-12 weeks)	RR 1.06; 95% CI, 0.95 to 1.19	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-12 weeks)	RR 0.55; 95% CI, 0.38 to 0.79)	High	Treatment with an SSRI decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-12 weeks)	RR 1.98; 95% CI, 1.51 to 2.61	High	SSRIs were more likely to cause discontinuations due to adverse events compared to placebo
SNRIs			
Treatment Response* (follow-up 8-24 weeks)	RR 1.34; 95% CI, 1.21 to 1.47	High	Treatment with SNRIs improved symptoms more than placebo
Total number of dropouts (follow-up of 8-28 weeks)	RR 1.03; 95% CI, 0.87 to 1.21	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-28 weeks)	RR 0.33; 95% CI, 0.25 to 0.43	High	Treatment with an SNRIs decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-28 weeks)	RR 2.42; 95% CI, 1.81 to 3.22	High	SNRIs were more likely to cause discontinuations due to adverse events compared to placebo
Other Antidepressants			
Treatment Response* (follow-up 8-12 weeks)	RR 1.54; 95% CI, 1.14 to 2.08	High	Treatment with 'other' antidepressants improved symptoms more than placebo
Total number of dropouts (follow-up of 8-12 weeks)	RR 0.90; 95% CI, 0.60 to 1.34	High	No difference between groups
Dropouts due to lack of efficacy (follow-up 8-12 weeks)	RR 0.52; 95% CI, 0.28 to 0.95	High	Treatment with 'other' antidepressants decreased the risk of dropping out of the study due to lack of efficacy
Dropouts due to adverse events (follow-up 8-12 weeks)	RR 2.29; 95% CI, 1.31 to 4.01	High	'Other' antidepressants were more likely to cause discontinuations due to adverse events compared to placebo
Key: * Treatments response was defined as a reduction in 50% or more on the HAM-A			

Abbreviations: CI = confidence interval; HAM-A = Hamilton Anxiety Rating Scale; RR = relative risk; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

AHRQ – Diagnosis and Management of Obsessive-Compulsive Disorder in Children

A 2025 review for the diagnosis and management of OCD in children and adolescents was done by AHRQ.² The review focused on assessment and diagnostic tools and efficacy and harms of treatments (behavioral and pharmacotherapy were evaluated). Literature was searched up to May 2024. The focus of this review will be on the evidence of pharmacological treatments, in which 24 studies were included, and behavioral and pharmacological treatment combinations which included 17 studies. Placebo-controlled comparisons included SSRIs (8 studies) and TCAs (2 studies).² Six studies compared a SSRI to a TCA. Outcomes were analyzed via a network meta-analysis.

The review found that treatment with SSRIs is more effective than placebo for reduction in OCD symptoms and global severity outcomes based on high quality evidence.² Exposure and response prevention (ERP) (i.e., cognitive behavioral therapy for OCD) is probably more effective than SSRIs for OCD symptom reduction based on moderate quality evidence. Combination ERP and SSRI treatment is as effective as ERP alone for symptom reduction and remission based on high quality evidence.² The TCA clomipramine is more effective than placebo for OCD symptoms based on moderate quality evidence. Studies comparing SSRIs to clomipramine found they were no differences in effectiveness (moderate quality evidence).² Evidence for harms of SSRIs and clomipramine were not fully reported making conclusions difficult.

After review, 26 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).^{25–34,27,35–43, 44–51}

New Clinical Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence – Headache

Guidance from NICE was updated in June 2025 for the diagnosis and management of headaches.³ This guidance updates a previous review done in September 2012. The focus of this guideline summary will be on the use of antidepressants for headache.

Amitriptyline is recommended for migraine prophylactic treatment.³ The continuing need for prophylaxis should be reassessed 3 to 6 months after initiating therapy. This recommendation is the same as previous guidance.

American College of Physicians – Prevention of Episodic Migraine: Pharmacologic Treatments in the Outpatient Setting

A 2025 guideline by ACP outlines treatment recommendations for the management of episodic migraines.⁴ Several classes of medications are evaluated. The focus of this review will be reviewing antidepressants used for migraine: SSRI (fluoxetine), SNRI (venlafaxine), and TCA (amitriptyline).

A systematic review and network meta-analysis were used to evaluate findings. Randomized clinical trials that were at least 12 weeks long and assessed the benefits and harms for episodic migraine prevention were evaluated.⁴ Most participants had an average of 7-8 headaches per month and had a history of

previous preventative migraine treatment failure.⁴ The certainty of evidence was graded from low to high and strength of recommendations are rated as strong (ACP recommends) and conditional (ACP suggests). Recommendations are for nonpregnant and nonlactating adults.

Monotherapy for episodic migraine prevention is recommended with a medication from one of the following classes based on a conditional recommendation supported by low-quality evidence: beta-adrenergic blocker (metoprolol or propranolol), valproate, venlafaxine or amitriptyline.⁴ No preference for one therapy over another was provided. Comparative evidence was limited; however, low certainty of evidence suggests that venlafaxine may reduce migraine duration compared to amitriptyline.⁴ There was insufficient evidence for the use of fluoxetine for the outcomes studied to draw strong conclusions of efficacy. Fluoxetine may be considered if there is intolerance or inadequate response to other recommended therapies.⁴

Adverse effects associated with antidepressants used for migraine are pain, paresthesia, reduced physical activity, rash and dizziness.⁴

NICE – Management of Bipolar Disorder

Guidance from NICE was updated in September 2025 on the management of bipolar disorder in children, young people and adults.⁵ Pharmacotherapy is recommended in adults who have moderate to severe bipolar depression. Fluoxetine combined with olanzapine or quetiapine monotherapy are recommended as the initial treatments of choice.⁵ Lamotrigine or olanzapine monotherapy can also be offered.⁵ If there is an inadequate response to fluoxetine combined with olanzapine, or quetiapine monotherapy, then lamotrigine monotherapy can be tried.⁵

SIGN – Management of Chronic Pain

An updated guideline on the management of chronic pain was completed by SIGN in 2019.⁶ Antiepileptics, non-opioid analgesics (NSAIDs and acetaminophen), topical capsaicin, topical lidocaine, topical rubefacients (i.e., methyl salicylate), opioids, and antidepressants were included in the guidance.⁶ Evidence was graded based on level of evidence (1+++[high quality] to 4 [expert opinion]) (**Table 5**) and grades of recommendation (A [high quality] to D [extrapolated evidence]).⁶

Table 5. SIGN Levels of Evidence⁶

LEVELS OF EVIDENCE	
1 ⁺⁺	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 ⁺	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Antidepressants with noradrenaline, serotonin and noradrenergic mechanisms of action, such as TCAs and SNRIs, have demonstrated superior efficacy to SSRIs for neuropathic pain.⁶ Tricyclic antidepressants were found to not be significantly different from placebo in pain relief in patients with chronic low back pain.

Evidence Supporting Guideline Recommendations (all based on high quality evidence):

- For the treatment of fibromyalgia, TCAs improved pain scores (SMD -0.43; 95% CI, -0.55 to -0.30; $p < 0.001$) and depression (SMD -0.26; 95% CI, -0.39 to -0.12; $p < 0.001$).⁶ Sleep disturbances and health-related quality of life (HRQOL) were also significantly improved with TCAs.⁶
- Amitriptyline reduced pain in patients with fibromyalgia (SMD -1.64; 95% CI, -2.57 to -0.71; $p < 0.001$) and sleep disturbances (weighted mean difference [WMD] -1.84; 95% CI, -2.62 to -1.06; $p < 0.001$).⁶
- Duloxetine 60-120 mg has been shown to be effective for the treatment of chronic low back pain based on bodily pain scores.⁶
- In patients with fibromyalgia, duloxetine produced better pain control compared to placebo for the outcome of 50% improvement (RR 1.60; 95% CI, 1.22 to 2.10; $p = 0.0007$) and 30% improvement (RR 1.52; 95% CI, 1.24 to 1.86; $p < 0.0001$).⁶
- Duloxetine and milnacipran reduced pain by 50% or more in patients with fibromyalgia compared to placebo (SMD -0.23; 95% CI, -0.29 to -0.18; p -value not provided).⁶
- Milnacipran 100 mg or 200 mg provided 30% or more pain relief compared to placebo in 40% patients with fibromyalgia. More adverse events occurred in the milnacipran group compared to placebo.⁶
- Duloxetine 60 mg reduced painful diabetic neuropathy with a 50% or more pain reduction with a NNT of 6 over 12 weeks.⁶
- Knee osteoarthritis was improved with duloxetine compared to placebo based on improvement of 30% or more in pain reduction (65.3% vs. 44.1%; $p \leq 0.001$). A 50% reduction in pain was not different between duloxetine and placebo.⁶
- Evidence from a meta-analysis found fluoxetine and paroxetine to be effective for pain relief in patients with fibromyalgia (SMD -0.39; 95% CI, -0.77 to -0.01; $p = 0.04$) (paroxetine only accounted for one study).⁶

Guideline Recommendations (All high-quality evidence and Grade A recommendation unless noted)

1. Duloxetine 60 mg daily should be considered in people with chronic pain.⁵²
2. Amitriptyline 25-125 mg daily should be considered for treatment of patients with fibromyalgia and neuropathic pain (excluding HIV-related neuropathic pain).⁶
3. Duloxetine 60 mg daily should be considered in patients with diabetic neuropathic pain if response is inadequate to first- or second-line therapies, such as lifestyle therapies and physical therapy.⁶
4. Duloxetine 60 mg daily should be considered in patients with fibromyalgia or osteoarthritis.⁶
5. Fluoxetine (20-80 mg daily) should be considered for the treatment of fibromyalgia (high quality evidence; Grade B recommendation).⁶
6. Adequate treatment of moderate depression in patients with chronic pain and comorbid depression should be considered.⁶
7. Combination therapy should be considered for patients with neuropathic pain, such as gabapentinoids, TCAs and SNRIs.⁶

MHCAG – Medication Treatment for Adults with Generalized Anxiety Disorders

In February of 2023 of the MHCAG created recommendations for the management of GAD.⁸ First-line treatment with escitalopram, sertraline, duloxetine, and venlafaxine XR are recommended for GAD symptom reduction and remission. The SSRIs, escitalopram and sertraline, are tolerated at higher doses compared to SNRIs.⁸ If first-line treatments are not effective or contraindicated then imipramine and bupropion XR can be considered. Adjunctive therapy may be required for adults with GAD. First-line adjunct treatment recommendations are for pregabalin, to be used with an SSRI or SNRI.⁸ There is low-quality evidence that

bupirone may be effective for GAD; however, it has a slow onset and frequent dosing limiting use. Additional adjunct treatment options are quetiapine XR, hydroxyzine, diazepam and lorazepam.⁸

MHCAG – Treatment of Chronic Insomnia Disorders in Adults

The MHCAG published recommendations for the treatment of chronic insomnia disorders in July of 2024.⁹ A key point in insomnia management is educate patients on sleep hygiene that may produce better sleep. Psychotherapy is recommended first line cognitive behavioral therapy for insomnia in person and online and mobile apps. If pharmacotherapy is needed then no more than 4 weeks is recommended.⁹ There are many classes of medications recommended for chronic insomnia treatment. Antidepressants that are recommended are doxepin (3-6 mg) and trazodone (50-150 mg).⁹ Other treatment options are lemborexant, suvorexant, eszopiclone and zolpidem. Short term use, 7-10 days of triazolam or temazepam can be tried.⁹

MHCAG – Recommendations on Extending Days' Supply for Mental Health Drugs

A review was done in March 2025 by the MHCAG on the benefits and risks of the current dispensing limits of 34 days per prescription claim for psychotropic medications.¹¹ While there is risk of intentional overdose (IOD) with 90-day supplies of mental health medications, there may be a benefit for some patients. The MHCAG recommends that a risk tool be published to assist providers in determining risk of IOD with psychotropic medications. The group recommended removal of the 34-day limit for non-controlled mental health drugs and controlled IV-V mental health drugs.¹¹

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

Table 6. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Paroxetine ⁵³	PAXIL	November 2024	Warnings and Precautions	Meta-analysis of epidemiological studies demonstrate exposure to paroxetine in the first trimester of pregnancy is associated with a less than 2-fold increase in the rate of cardiovascular malformations among infants. Paroxetine should be initiated only after consideration of other treatment options for women who intend to become pregnant or who are in their first trimester of pregnancy.
Amitriptyline/ chlordiazepoxide ⁵⁴	LIMBITROL	June 2025	Warnings and Precautions	Risk of serotonin syndrome alone and more commonly when used with other serotonergic drugs and with drugs that impair the metabolism of serotonin. Hyponatremia has also been reported often due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Bupropion and bupropion SR ⁵⁵	WELLBUTRIN	August 2025	Warnings and Precautions	Risk of aseptic meningitis.

	WELLBUTRIN SR			
Desipramine ⁵⁶	NORPRAMIN	June 2025	Warnings and Precautions	Risk of hyponatremia has been reported often due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Doxepin ⁵⁷	SINEQUAN	July 2025	Boxed Warnings	Increased risk of suicidal thoughts and behaviors in pediatric and young adults taking antidepressants. Doxepin is not approved in pediatric patients.

Randomized Controlled Trials:

A total of 355 citations were manually reviewed from the initial literature search. After further review, citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Janik, et al ⁵⁸ DB, PC, Phase 4, RCT	Esketamine NS 56 mg monotherapy twice weekly x 4 weeks* Esketamine NS 84 mg monotherapy twice weekly x 4 weeks* Placebo NS twice weekly x 4 weeks	Adults with MDD without psychotic features who experienced an inadequate response ($\leq 25\%$ improvement) to ≥ 2 oral antidepressants during current depressive episode (n=378)	Change in MADRS from baseline at day 28	Esketamine 56 mg: -12.7 Esketamine 84 mg: -13.9 Placebo: -7.0 Esketamine 56 mg vs. Placebo LSMD -5.1 (95% CI, -7.91 to -2.33; p<0.001) Esketamine 84 mg vs. Placebo LSMD -6.8 (95% CI, -9.48 to -4.07; p<0.001)	Mean baseline MADRS score was 37.3 indicating severe depression. Onset of esketamine efficacy around 24 hours. Results were clinically meaningful with a MADRS change greater than 2. Limitations included short study duration, exclusion of patients with other mental health comorbidities, and possible unblinding due to adverse effects of esketamine. Adverse events were similar between groups.

Key: * Fixed doses of esketamine with no option for titration.

Abbreviations: CI = confidence interval; DB = double blind; LSMD = least-square mean difference; MADRS = Montgomery-Asberg Depression Rating Scale Total Score; MDD = major depressive disorder; NS = nasal spray; PC = placebo-controlled; RCT = randomized clinical trial.

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y

escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nefazodone HCl	NEFAZODONE HCL	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
dextromethorphan HBr/bupropion	AUVELITY	TAB IR ER	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	CAPSULE	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
gepirone HCl	EXXUA	TAB ER 24H	V

imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANLYCYPROMINE SULFATE	TABLET	V
trazodone HCl	RALDESY	SOLUTION	V
trazodone HCl	TRAZODONE HCL	TABLET	V
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
zuranolone	ZURZUVAE	CAPSULE	V
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	

Miscellaneous Agents for Depression, Anxiety, and Fibromyalgia

<u>Generic</u>	<u>Brand</u>	<u>Form</u>
buspirone HCl	BUCAPSOL	CAPSULE
buspirone HCl	BUSPIRONE HCL	TABLET
lithium carbonate	LITHIUM CARBONATE	CAPSULE
lithium carbonate	LITHIUM CARBONATE	TABLET
lithium carbonate	LITHIUM CARBONATE ER	TABLET ER
lithium carbonate	LITHOBID	TABLET ER
lithium citrate	LITHIUM CITRATE	SOLUTION
milnacipran HCl	SAVELLA	TAB DS PK
milnacipran HCl	SAVELLA	TABLET

Appendix 2: Abstracts of Comparative Clinical Trials

Esketamine Monotherapy in Adults With Treatment-Resistant Depression: A Randomized Clinical Trial

Janik, Xin Qiu, Rosanne Lane, Vanina Popova, Wayne C Drevets, Carla M Canuso, Matthew Macaluso, Gregory W Mattingly, Richard C Shelton, John M Zajecka, Dong-Jing Fu

Importance: Esketamine nasal spray, administered in conjunction with an oral antidepressant, is approved for treatment-resistant depression (TRD). However, the efficacy of esketamine nasal spray administered as monotherapy for patients with TRD has not yet been evaluated.

Objective: To assess the efficacy and safety of esketamine monotherapy compared to placebo in reducing depressive symptoms in patients with TRD.

Design, setting, and participants: This phase 4, double-blind, placebo-controlled randomized clinical trial was conducted from November 2020 to January 2024 at 51 outpatient centers in the US. Adults with major depressive disorder (DSM-5 criteria) without psychotic features who experienced inadequate response ($\leq 25\%$ improvement) to 2 or more oral antidepressants during the current depressive episode were eligible for inclusion. Data analyses were conducted from March 1, 2024, to July 8, 2024.

Interventions: After a 2-week or longer antidepressant-free period, participants were randomized at a 1:1:2 ratio to fixed-dose intranasal esketamine (56 mg or 84 mg) or matching intranasal placebo, administered twice weekly for 4 weeks.

Main outcomes and measures: Change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to day 28 (primary efficacy end point) and to 24 hours post-first dose (day 2; key secondary efficacy end point) were analyzed by a mixed-effects model using repeated measures.

Results: In this multicenter randomized clinical trial, 378 participants who met prerandomization MADRS severity criteria received 1 or more study drug doses (esketamine, 56 mg [$n = 86$]; esketamine, 84 mg [$n = 95$]; or placebo [$n = 197$]). Mean (SD) participant age was 45.4 (14.1) years, 231 participants (61.1%) were female, and baseline mean (range) MADRS total score was 37.3 (28-50). At day 28, the least-square (LS) mean difference (SE) between esketamine and placebo was -5.1 (1.42) (95% CI, -7.91 to -2.33) for the 56-mg dose and -6.8 (1.38) (95% CI, -9.48 to -4.07) for the 84-mg dose (for each, 2-sided $P < .001$). Observed effect sizes were 0.48 and 0.63 for the 56-mg and 84-mg dose groups, respectively. At day 2 (approximately 24 hours post-first dose), the between-group difference was significant for both esketamine doses: -3.8 (1.29) (95% CI, -6.29 to -1.22; 2-sided $P = .004$) for 56 mg and -3.4 (1.24) (95% CI, -5.89 to -1.00; 2-sided $P = .006$) for 84 mg. The most common treatment-emergent adverse events reported for esketamine (combined doses) were nausea (56 participants [24.8%]), dissociation (55 [24.3%]), dizziness (49 [21.7%]), and headache (43 [19.0%]).

Conclusions and relevance: According to results of this multicenter, double-blind randomized clinical trial, esketamine monotherapy may expand treatment options for adult patients with TRD by addressing an unmet need of patients experiencing treatment-limiting tolerability concerns and nonresponse with oral antidepressants.

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to October 24, 2025
Search Strategy:

#	Searches	Results
1	Amitriptyline/ or amitriptyline.mp.	10333
2	bupropion.mp. or Bupropion/	6145

3	citalopram.mp. or Citalopram/	8180
4	desipramine.mp. or Desipramine/	8052
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	604
6	duloxetine.mp. or Duloxetine Hydrochloride/	3731
7	doxepin.mp. or Doxepin/	1589
8	escitalopram.mp. or Escitalopram/	3788
9	fluoxetine.mp. or Fluoxetine/	16694
10	Fluvoxamine.mp. or Fluvoxamine/	3508
11	imipramine.mp. or Imipramine/	13717
12	mirtazapine.mp. or Mirtazapine/	3036
13	nefazodone.mp.	821
14	nortriptyline.mp. or Nortriptyline/	3397
15	paroxetine.mp. or Paroxetine/	7217
16	sertraline.mp. or Sertraline/	6709
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	5429
18	amoxapine.mp. or Amoxapine/	499
19	clomipramine.mp. or Clomipramine/	4221
20	dextromethorphan.mp. or Dextromethorphan/	3391
21	esketamine.mp.	1642
22	isocarboxazid.mp. or Isocarboxazid/	424
23	levomilnacipran.mp. or Levomilnacipran/	117
24	phenelzine.mp.	1709
25	protriptyline.mp. or Protriptyline/	419
26	selegiline.mp. or Selegiline/	3093
27	tranylcypromine.mp. or Tranylcypromine/	2353

28	trimipramine.mp. or Trimipramine/	555
29	vilazodone.mp. or Vilazodone Hydrochloride/	312
30	vortioxetine.mp. or Vortioxetine/	879
31	trazodone.mp. or Trazodone/	2556
32	gepirone.mp.	310
33	zuranolone.mp.	146
34	buspirone.mp. or Buspirone/	3226
35	lithium.mp. or Lithium/	85025
36	milnacipran.mp. or Milnacipran/	826
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	176189
38	limit 37 to (english language and humans and yr="2024 -Current")	3426
39	limit 38 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	355

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for antidepressant use (e.g., depression, anxiety, pain)
Intervention	Antidepressant treatment
Comparator	Placebo or active treatment comparison
Outcomes	Reduction in symptoms of depression, pain, anxiety
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Author: Sentena

Tricyclic Antidepressants

Goal(s):

- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
 - Patients with a claim for an SSRI or TCA in the last 6 months
 - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications of Tricyclic Antidepressants in Children

Drug	FDA-Approved Indications	Maximum Daily Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg (150 mg for 10-19 years of age)	10
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression	225 mg	18

	Dysthymia Mixed anxiety and depressive disorder		
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the dose exceed the maximum FDA-approved dose (Table 1)?	Yes: Go to #3	No: Go to #4
3. Is there documentation that the prescriber is monitoring blood levels to support use of the prescribed dose?	Yes: Go to #4	No: Go to #6
4. Is the request for an FDA-approved indication and age (Table 1)?	Yes: Approve for up to 6 months	No: Go to #5
5. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	Yes: Approve for up to 6 months	No: Go to #6
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	Yes: Approve for up to 6 months	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 2/26; 6/24 (KS); 12/23, 2/23, 2/21(SS) 11/19
Implementation: 7/1/24; 2/1/2020

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment-resistant depression or suicidal ideation.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	Yes: Go to Renewal Criteria	No: Go to #4
4. Is the patient 65 years or older?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria

6. Is there prescriber attestation or documentation of treatment-resistant depression based on all the following criteria: a. Diagnosis of unipolar major depressive disorder b. Patient has tried at least 2 different antidepressants in which: i. There has been inadequate response after at least 6 weeks of treatment at an average minimum therapeutic dose or greater; or ii. The patient has not been able to continue treatment for at least 6 weeks due to intolerable side effects. Minimum therapeutic doses can be found here: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf	Yes: Go to #9	No: Go to #7
7. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
8. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: - Titrating the dose of the current antidepressant to a therapeutic level - Switching to a different antidepressant OR - Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness.
9. Does the patient have documentation of any of the following: - Current Aneurysmal vascular disease or arterial venous malformation OR - History of Intracerebral hemorrhage OR - Current Pregnancy OR - Current Uncontrolled hypertension (e.g., >140/90 mmHg)	Yes: Pass to RPh. Deny; medical appropriateness.	No: Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	Yes: Go to #2	No: Go to #3
2. Is the request for administration of esketamine once weekly or every 2 weeks?	Yes: Approve for up to 6 months (maximum of 12 per 28 days)	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. Has the patient been on therapy for at least 4 weeks?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Approve for completion of induction phase (total 28 days of treatment with a maximum of 24 nasal spray devices (each device contains 28 mg of esketamine))

P&T/DUR Review: 2/26); 6/25(SS);6/24(KS);2/24; 12/23; 2/23, 10/21; 2/21; 7/19
Implementation 8/1/25; 7/1/24; 1/1/22; 3/1/21; 8/19/19

Zuranolone (Zurzuvae)

Goal(s):

- To ensure appropriate use of zuranolone in patients with post-partum depression.

Length of Authorization:

- One time use only.

Requires PA:

- Zuranolone requires a prior authorization approval due to safety concerns.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and age (e.g., ≥18 years)?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Does the patient have moderate to severe post-partum depression? Note: Zuranolone is not indicated for major depressive disorder but can be covered for depression meeting the clinical diagnosis of post-partum depression (e.g., moderate to severe depression with peripartum onset).	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with zuranolone for severe post-partum depression related to their most recent pregnancy?	Yes: Pass to RPh. Deny; medical appropriateness. Multiple courses of zuranolone have not been studied.	No: Approve for a single 14-day treatment.

P&T/DUR Review: 2/26; 6/24 (KS); 12/23
Implementation: 1/1/24

Milnacipran

Goal(s):

- Restrict use to OHP-funded and evidence-supported diagnoses.

Length of Authorization:

- Up to 12 months

Requires PA:

- Milnacipran

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for renewal of previously approved milnacipran therapy?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the diagnosis an OHP-funded diagnosis (see Table 1 below)?	Yes: Go to #4	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded. If eligible for EPSDT review: Go to #4
4. Is this an FDA approved or evidence-supported indication and age (see Table 1 below)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Has the patient had an inadequate response (i.e., appropriate dose and duration of at least 6-8 weeks) and/or intolerance/contraindication to 2 preferred treatments?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness. Recommend a trial of amitriptyline or duloxetine

Renewal Criteria		
1. Is there provider attestation of a reduction or stabilization in pain symptoms related to fibromyalgia since starting milnacipran?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness. Recommend alternative therapy for pain control.

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	
Diabetic Neuropathy	
Postherpetic Neuropathy	

Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	≥18 years

P&T Review: 2/26 (KS); 7/18 (DM); 3/17
Implementation: 4/1/17



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New Drug Evaluation: Tryngolza™ (Olezarsen) injection

Date of Review: February 2026

Generic Name: Olezarsen

End Date of Literature Search: 11/15/2025

Brand Name (Manufacturer): Tryngolza (Ionis Pharmaceuticals, Inc)

Dossier Received: yes

Plain Language Summary:

- Olezarsen is a new medicine used to reduce triglyceride levels in patients with a genetic condition causing very high triglyceride levels. This condition is called familial chylomicronemia syndrome. Patients with a very high triglyceride level (≥ 1000 mg/dl) are at an increased risk for certain complications, including stomach pain and inflammation of the pancreas, known as pancreatitis.
- No other medications reduce triglyceride levels in this condition. Dietary and fat restrictions are currently the only recommended treatments. These dietary restrictions are difficult for patients to maintain.
- In one study, olezarsen injected subcutaneously, or under the skin, once a month reduced triglyceride levels by a meaningful amount when compared to placebo over 6 months in patients who were also following a low-fat diet. We do not know much olezarsen reduces risk of pancreatitis in patients with familial chylomicronemia syndrome.
- Side effects with olezarsen include a decreased platelet count and increased liver enzymes. This is important because platelets help stop bleeding and high liver enzymes is a sign of liver inflammation that can lead to liver damage.
- We recommend olezarsen will be covered for people with familial chylomicronemia syndrome who are enrolled in the fee-for-service Oregon Health Plan after a prior authorization request by the prescriber is approved.

Research Questions:

1. Is there evidence demonstrating the efficacy of olezarsen in reducing triglyceride (TG) levels and episodes of acute pancreatitis in patients with Familial Chylomicronemia Syndrome (FCS)?
2. Is there evidence that olezarsen is safe for reducing TG levels and episodes of acute pancreatitis in patients with FCS?
3. Are there specific subpopulations for which olezarsen is better tolerated or more effective when used for FCS?

Conclusions:

- There is low-quality evidence that olezarsen 80 mg subcutaneous (SC) once monthly lowers TG levels significantly more than placebo at 6 months (least squares mean [LSM] difference -43.5%; 95% confidence interval [CI] -69.1 to -17.9; $p < 0.001$) in participants with FCS. While there is biologic plausibility that this reduction will decrease risk for in acute pancreatitis and there was a nominal decrease in pancreatitis in the phase 3 study, there remains insufficient data showing a benefit in lowering pancreatitis in FCS.

- There is limited long-term data demonstrating safety of olezarsen. Safety concerns include elevated hepatic transaminases, thrombocytopenia and associated bleeding. There was an increase in mild thrombocytopenia without serious bleeding in clinical studies and patients with thrombocytopenia at baseline were excluded. This will need to be monitored in clinical practice and more long-term safety data is needed to better define the risk with olezarsen.
- There is supportive data that olezarsen 50 mg and 80 mg reduce TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dl) at high cardiovascular (CV) risk and severe hypertriglyceridemia (TG level $\geq$ 500 mg/dl) without FCS on background lipid lowering therapy. At the time of this review, olezarsen is not FDA approved for this indication.

Recommendations:

- Make olezarsen as non-preferred in the “*Other Dyslipidemia Drug*” preferred drug list (PDL) class.
- Include clinical prior authorization criteria to ensure olezarsen is used according to supporting evidence and FDA labeling (**Appendix 3**).

Background:

Familial chylomicronemia syndrome is a rare autosomal recessive genetic disorder that causes a deficiency in lipoprotein lipase (LPL) enzyme activity through inactivation of the LPL gene resulting in persistence of triglyceride rich chylomicrons.¹ Although the onset of symptoms usually occurs in childhood or adolescence, FCS is often underdiagnosed or the diagnosis is delayed and up to 30% of patients with FCS remain undiagnosed until adulthood. FCS affects an estimated 1 to 13 individuals per 1,000,000 in the United States and is characterized by severely elevated chylomicrons and plasma triglycerides (TGs) and an increased risk of pancreatitis.^{1,2} Clinical presentation includes a TG level greater than 885 mg/dl repeatedly, or greater than 1000 mg/dl, lack of response to standard treatments, and history of acute pancreatitis. Patients have a 60% to 90% lifetime risk of pancreatitis. There is often a lack of other secondary risk factors, such as obesity and diabetes. Other manifestations can include eruptive cutaneous xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly.^{1,2}

Genetic testing remains the gold standard for diagnosing FCS. The North American Familial Chylomicronemia Score (NAFCS) calculator was developed to use clinical criteria to determine a diagnosis of FCS and may be useful for patients who have not been tested genetically or in whom genetic testing was inconclusive.¹ It is recommended only when patients are not responsive to fibrates and high-dose omega-3 fatty acids (< 20% reduction in TGs). The NAFCS calculator includes the following variables: young age of onset, BMI less than 25 kg/m², history of abdominal pain or pancreatitis, absence of secondary risk factors, persistent fasting TG greater than 885 mg/dl, TG to total cholesterol ratio greater than 3.5 mg/dl, apoB < 1 g/L, and nonresponse to conventional medications.¹

The goal of treatment in FCS is to prevent acute pancreatitis and reduce plasma TG levels to less than 885 mg/dl. There is no current evidence-based definitive TG target and there are no high-quality clinical guidelines addressing FCS. There are currently no FDA approved treatments for FCS. Standard triglyceride-lowering treatments with fibrates, niacin, and omega-3 fatty acids are typically not effective in FCS due to a lack of LPL activity in FCS patients. Standard of care remains a restrictive low-fat diet (< 20 grams daily) to reduce the accumulation of chylomicrons, complete avoidance of alcohol, and physical activity. While standard lipid-lowering drugs are generally not effective for patients with FCS as they have no impact on chylomicron metabolism, they may be beneficial in patients with concomitant risk factors for atherosclerotic cardiovascular disease (ASCVD).^{1,2}

Olezarsen is the first FDA-approved treatment for FCS and is an antisense oligonucleotide targeting apolipoprotein C-III (APOC3) mRNA to reduce APOC3 production. Olezarsen was FDA approved through expedited approval pathways, including fast track, breakthrough therapy, and priority review.² Inhibiting

APOC3 may reduce TG levels by enhancing LPL activity and reducing serum apolipoprotein C-III protein, a key regulator of TG metabolism. Volanesorsen is an APOC3 inhibitor approved in Europe for the treatment of FCS. It was not approved in the United States because of concerns about thrombocytopenia.¹ Olezarsen is a second generation APO3 inhibitor targeting hepatic APOC3 mRNA. It has the same chemical composition as volanesorsen but differs with the addition of a triantennary N-acetyl galactosamine, which allows for lower dosing. It was approved by the FDA for the treatment of FCS in adults and has been studied in moderate to severe hypertriglyceridemia. Piloasiran is a small interfering RNA (siRNA) targeting hepatic APOC3 mRNA that was recently FDA approved and will be brought back for review.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:

Clinical trials used to support FDA approval are described and evaluated below in **Table 1**.

Olezarsen received FDA approval based on one randomized, phase 3, double-blind, controlled trial comparing olezarsen 50 mg SC once monthly, olezarsen 80 mg SC once monthly, and placebo in adults 18 years of older with FCS and fasting TG levels greater than 880 mg/dl with and without a history of pancreatitis.³ The FDA typically requires two adequate and well controlled trials to provide substantial evidence for efficacy. However, the FDA allowed one study due to the rarity of the condition and lack of alternative treatment options for FCS.²

In the phase 3 randomized controlled trial (RCT), patients underwent genetic testing to confirm loss-of-function variants and a diagnosis of FCS. If the patient was not already following a low-fat diet, they were enrolled in a 2-week dietary run-in period. Patients were instructed to consume no more than 20 g of fat per day, and alcohol use was discouraged. Patients were randomized to olezarsen 50 mg (n=21), 80 mg (n=22), or placebo (n=23).³ The primary outcome was change from baseline in fasting TG level at 6 months.

Of the 144 participants screened, 66 (46%) were eligible for randomization. There was a statistically significant difference in percent change in fasting TG level from baseline to 6 months between olezarsen 80 mg and placebo (least-squares mean [LSM] reduction of 43.5%; 95% confidence interval [CI] -69.1 to -17.9; $p < 0.001$).³ However, there was no significant difference between olezarsen 50 mg and placebo (LSM -22.4%; 95% CI -47.2% to 2.5; $p = 0.08$) at 6 months.³ There were 7 events of acute pancreatitis in the placebo group (30.4%) compared to 2 in the pooled olezarsen group (4.7%) (rate ratio 0.12; 95% CI 0.02 to 0.66).³

There are important limitations to consider in this study. Differences in baseline characteristics increase the risk of selection bias. In this RCT there was a higher percentage of patients with a history of acute pancreatitis in the olezarsen groups compared to placebo, more white patients in the placebo group, more participants from North America in the placebo group, and more participants ≥ 65 years of age in the placebo group.³ All study participants were required to follow strict dietary restrictions, and it is unclear how much dietary changes impacted the results. Since the 50 mg comparison was not significant, the hierarchical design of the study limited statistical comparison for the secondary outcomes and conclusions cannot be made regarding these outcomes, including acute pancreatitis and changes in other lipoproteins. The magnitude of benefit on TG reduction was lower than what the authors predicted and used to power the study. Lastly, the outcome assessors included probable and possible cases of acute pancreatitis as pancreatitis episodes in the study.

A phase IIb randomized, controlled study in adults with either moderate hypertriglyceridemia (TG 150-499 mg/dl) and elevated CV risk or with severe hypertriglyceridemia (TG $\geq$ 500 mg/dl) was used by the FDA as a confirmatory study.⁴ Of the 304 participants screened, 49% failed screening, related to extensive inclusion and exclusion criteria and 92% of patients were white. This limits the generalizability of the study results. Most patients did not have clinical ASCVD and had moderate hypertriglyceridemia (90%) with a TG level less than 500 mg/dl. There was a significant reduction in TG levels at 6 months in both olesarsen 50 mg (treatment difference 49.3%; 95% CI 39.5 to 59) and olesarsen 80 mg (treatment difference 53.1%; 95% CI 43.4 to 62.9) groups and more patients in each olesarsen group achieved a TG level less than 150 mg/dl compared to placebo.⁴

Since FDA approval, additional phase 3 trials have been published in patients with hypertriglyceridemia without FCS. In two large phase 3, multicenter, double-blind, RCTs with identical designs, patients with severe hypertriglyceridemia (fasting TG level of at least 500 mg/dl) were randomized to receive olesarsen 50 mg, olesarsen 80 mg, or placebo for 48 weeks (n=1063).⁵ The median age across both trials was 54 years and only 23.6% were women. A total of 88.4% of participants were white and almost all patients were on at least one lipid-lowering medication with 64% receiving a fibrate.⁵ Treatment with olesarsen resulted in a statistically significant greater reduction in the triglyceride level at 6 months compared to placebo across both trials with a placebo-adjusted difference from baseline of -49.2% and -62.9% in the olesarsen 50 mg group and a difference of -72.2% and -54.5% in the olesarsen 80 mg group. The reduction in TG levels was maintained through 12 months. Across both trials, there was a reduction in acute pancreatitis episodes with pooled olesarsen doses compared to placebo (7 episodes vs. 22 episodes) with a rate ratio of 0.15; 95% CI 0.05 to 0.40).⁵ The results were similar in patients with moderate hypertriglyceridemia (TG level 150 to 400 mg/dl) and elevated CV risk (LSM change in TG level of -58.4%; 95% CI -65.1% to -51.7% in olesarsen 50 mg and -60.6%; 95% CI -67.1 to -54% in olesarsen 80 mg compared to placebo).⁶

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Acute pancreatitis
- 2) Hospitalization due to pancreatitis
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event
- 5) Reduction in TG level

Primary Study Endpoint:

- 1) Percent change in fasting triglyceride level from baseline to 6 months (average of weeks 23, 25, and 27)

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR /NN T	Safety Outcomes	ARR/N NH	Risk of Bias/ Applicability
Stroes, et al. ³ 2024 BALANCE NCT045684 34 PC, DB, MC, phase 3 RCT	1. Olezarsen 80mg SC every 4 weeks 2. Olezarsen 50mg SC every 4 weeks 3. Placebo SC every 4 weeks * Diet stabilization for 2 weeks with 2-week qualification period: prior to therapy start 53 weeks	Demographics: -Median Age 45 years old -Female 52.2% -Ethnicity White 84.8% -History of pancreatitis: 71% -Baseline TG 2630 mg/dL Key Inclusion Criteria: -Genetically confirmed diagnosis of FCS -Fasting TG ≥880 mg/dL -Age ≥18 years old - ≤ 20g of fat per day diet - Non-pregnant, non-lactating and surgically sterile, postmenopausal, abstinent, or on highly effective contraceptive Key Exclusion Criteria: -Clinically significant abnormalities in medical history or physical examination -Active pancreatitis -Platelets < 100,000 - AST/ALT > 3 x ULN -eGFR < 45 ml/min - Uncontrolled hypertension - History of bleeding diathesis or coagulopathy - Malignancy within 5 years - Active infection with HIV, HCV, or HBV	ITT: 1.22 2.21 3.23 PP: 1.18 2.19 3.22 Attrition: 1. 3 (13.6%) 2. 2 (9.5%) 3. 1 (4.3%)	Primary Endpoint: Percent change in fasting TG from baseline at Month 6 1. -33.3% 2. -10.3% 3. 11.2% Mean difference: 80 mg vs placebo: -43.5% 95% CI, -69.1 to -17.9; P<0.001 50 mg vs. Placebo: -22.4%; 95% CI, -47.2 to 2.5; P=0.08 Secondary Endpoint: * Mean change in fasting TG from baseline to 12 months 1. -39.7% 2. -21.5% 3.: 21.6% Treatment difference: 80 mg vs. Placebo: -59.4%; 95% CI -90.7 to -28.1 50 mg vs. Placebo: -43.8%; 95% CI -73.9% to -13.7% Acute Pancreatitis 1. 1 (4.5%) 2. 1 (4.8%) 3. 7 (30.4%) Pooled olezarsen vs. Placebo: RR 0.12; 95% CI 0.02 to 0.66 Secondary endpoints considered exploratory due to hierarchical design and lack of statistical finding for second	NA NS NA NA	Discontinuations due to AE: 1. 2 (9.1%) 2. 1 (4.8%) 3. 0 SAE: 1. 3 (14%) 2. 4 (19%) 3. 9 (39%)	NS	Risk of Bias (low/high/unclear): Selection Bias: Unclear; Randomization was performed using an interactive response technology system. Some differences in baseline characteristics. Performance Bias: Low; double blinded using matching volume of placebo. Detection Bias: Unclear; outcome assessors blinded for adjudication of pancreatitis events; large treatment difference in triglyceride levels could result in unblinding. Attrition Bias: Low; low attrition rates (<10%), ITT analysis used for primary outcome. Reporting Bias: Low. Protocol available online and all outcomes prespecified. Other Bias: High. Study financially supported by drug manufacturer. Ionis Pharmaceuticals involved in data interpretation and preparation of manuscript. Applicability: Patient: Rare disease limits sample size. 54% of screened patients did not meet randomization criteria. FCS is often present in adolescents, who were excluded. Intervention: Doses selected based on phase 2 study in ASCVD and expected reduction in TG with each dose. Reductions in study are smaller than what was expected. Only the 80 mg is FDA approved. Comparator: Placebo group comparator appropriate since no other approved treatments are available. Outcomes: Reduction in TG levels is a surrogate outcome. Uncertainty around magnitude of benefit on acute pancreatitis. Included 28 secondary outcomes. Setting: 29 sites in US, Canada, EU and UK. 19/66 patients are from the US.

				primary endpoint; p values not reported				
Bergmark, et al. ⁴ 2024	1. Olezarsen 80mg SC every 4 weeks	Demographics: Mean age: 62 y/o 90% with TG < 500 mg/dl 42% women 92% white	ITT: 1.57 2.58 3.39	Primary Endpoint: Percent change in TC levels from baseline to 6 months 1. -60.9% 2. -57.1% 3. -7.8%		DC due to AE: 4. 3 (5%) 5. 7 (12%) 6. 0	NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Unclear; unclear randomization and allocation concealment; proportion of women lower in olezarsen group, more patients in placebo group were taking a fibrate.
Bridge-TIMI 73a	2. Olezarsen 50mg SC every 4 weeks	97% on lipid lowering therapy Median TG 241.5 mg/dl	PP: 1.49 2.50 3.38	Mean difference: 80 mg vs placebo: -53.1% 95% CI, -43.4 to 62.9; P<0.001	NA	SAE: 4. 7 (12%) 5. 4 (7%) 6. 2 (5%)	NA	<u>Performance Bias:</u> Low; double blinded using matching placebo volume.
NCT053554 02	3. Placebo SC every 4 weeks	Key Inclusion Criteria: -TG 150-499 mg/dl with either clinical ASCVD or an increased ASCVD risk OR TG ≥ 500 mg/dl -Stable lipid lowering therapy	Attrition: 1. 2% 2. 5% 3. 0%	50 mg vs. Placebo: -49.3% 95% CI, -39.5 to -59; P<0.001	NA			<u>Detection Bias:</u> Unclear; unclear blinding of outcome assessors.
PC, MC, phase 2 RCT	*on stable lipid-lowering therapy 53 weeks	Key Exclusion Criteria: -HbA1C ≥ 9.5% - ACS/TIA within 6 months - Active pancreatitis in last 4 weeks - AST/ALT > 3 x ULN -eGFR < 30 ml/min - Uncontrolled hypertension - Malignancy within 5 years - active infection with HIV, HCV, or HBV		Secondary Endpoints: TG level of < 150 mg/dl 1. 93% 2. 86% 3. 12% P< 0.001 for both comparisons 95 CI NR	NA			<u>Attrition Bias:</u> Low; low overall attrition and similar between groups. <u>Reporting Bias:</u> Low. Protocol available online and all outcomes prespecified. <u>Other Bias:</u> High; funded by Ionis pharmaceuticals
								Applicability: <u>Patient:</u> 8-week screening period including diet/lifestyle stabilization and qualification period limits applicability. ~50% of those screened did not meet inclusion/exclusion criteria. 90% of patients were white. <u>Intervention:</u> TG lowering therapy. Unclear dose response based on this study. <u>Comparator:</u> Placebo controlled; lack of active comparator <u>Outcomes:</u> TG lowering is a surrogate outcome; unclear impact on CV outcomes <u>Setting:</u> 28 sites in North America

Abbreviations : ACS = acute coronary syndrome; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; CI = confidence interval; CV = cardiovascular; DC = discontinuation; DB = double-blind; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITT = intention to treat; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RR: rate ratio; SAE = serious adverse events; SC = subcutaneous; TG = triglyceride; ULN = upper limit of normal.

Clinical Safety:

In the primary phase 3 study, the most common adverse events that occurred more frequently with olezarsen compared to placebo were injection site reactions, thrombocytopenia, and arthralgia (**Table 2**). Discontinuations due to adverse events were 7% in the pooled olezarsen group and 0% in placebo. Safety concerns with olezarsen include thrombocytopenia and bleeding, injection site reactions, and hepatic adverse events.

Table 2: Adverse reactions that occurred in > 5 % of patients and at a higher frequency than placebo

Adverse reaction	Olezarsen (n=43)	Placebo (n=23)
Injection site reactions	8 (19%)	2 (9%)
Decreased platelet count	5 (12%)	1 (4%)
Arthralgia	4 (9%)	0

Due to safety concerns regarding thrombocytopenia with volanesorsen, bleeding and thrombocytopenia is a concern for olezarsen. In clinical trials more participant on olezarsen experienced platelet reductions compared to placebo. Although none were categorized as severe, the study excluded patients with platelet counts < 100 x 10⁹/L at baseline so it remains unknown if serious thrombocytopenia will occur. There was no increased risk of major bleeding with olezarsen compared to placebo.

In the larger phase 3 studies in patients without FCS, there were more frequent elevations in liver transaminases and thrombocytopenia with the 80 mg dose of olezarsen, suggesting a dose response for adverse reactions. Increases in glycated hemoglobin levels were also observed with both doses among patients with diabetes.

References:

1. Javed F, Hegele RA, Garg A, et al. Familial chylomicronemia syndrome: An expert clinical review from the National Lipid Association. *J Clin Lipidol*. 2025;19(3):382-403.
2. FDA Integrated Review. Tryngolza (olezarsen). 12/2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218614Orig1s000IntegratedR.pdf.
3. Stroes ESG, Alexander VJ, Karwadowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *The New England journal of medicine*. 2024;390(19):1781-1792.
4. Bergmark BA, Marston NA, Prohaska TA, et al. Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk. *The New England journal of medicine*. 2024;390(19):1770-1780.
5. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk. *The New England journal of medicine*. 2025.
6. Bergmark BA, Marston NA, Prohaska TA, et al. Targeting APOC3 with Olezarsen in Moderate Hypertriglyceridemia. *The New England journal of medicine*. 2025;393(13):1279-1291.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRYNGOLZA safely and effectively. See full prescribing information for TRYNGOLZA.

TRYNGOLZA (olezarsen) injection, for subcutaneous use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

TRYNGOLZA is an *APOC-III*-directed antisense oligonucleotide (ASO) indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of TRYNGOLZA is 80 mg administered subcutaneously once monthly. (2.1)
- Administer TRYNGOLZA into the abdomen or front of the thigh. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 80 mg/0.8 mL in a single-dose autoinjector. (3)

CONTRAINDICATIONS

History of serious hypersensitivity reactions to olezarsen or any of the excipients in TRYNGOLZA. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions have been reported in patients treated with olezarsen. Advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of TRYNGOLZA if hypersensitivity reactions occur. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (incidence >5% of TRYNGOLZA-treated patients and >3% higher frequency than placebo) were injection site reactions, decreased platelet count, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals Inc. at toll free number 1-833-644-6647 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Olezarsen is an antisense oligonucleotide targeting messenger RNA for apolipoprotein C-III (apoC-III) of which regulates triglyceride levels. Additionally, olezarsen has a conjugated ligand three N-acetyl-galactosamine (GalNAc) residue to facilitate target delivery to liver cells. Reduction in apoC-III protein leads to decreased triglyceride and very low-density lipoprotein.
Oral Bioavailability	Subcutaneous administration; not applicable
Distribution and Protein Binding	91.0 L central Vd, 2960 L peripheral Vd; Protein binding = >99%
Elimination	Urinary excretion (<1%) after 24 hours
Half-Life	Approximately 30 days
Metabolism	Metabolized by endo-and exonucleases to short oligonucleotide fragments of varying sizes within the liver. Oligonucleotides are not part of the CYP metabolic pathways.

Abbreviations: CYP = cytochrome P450; L=liters; Vd= Volume of distribution.

Appendix 3: Proposed Prior Authorization Criteria

APOLIPOPROTEIN C-III (APOC3) Inhibitors

Goal(s):

- Promote use of APOC3 Inhibitors that is consistent with medical literature.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- Olezarsen (Tryngolza)
- Plozasiran (Redemplo)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the prescriber a specialist in lipid management?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Does the patient have a diagnosis of familial chylomicronemia syndrome (FCS), confirmed by genetic testing? Please submit a copy of the genetic testing results	Yes: Go to #5	No: Go to #7
5. Does the patient have a current triglyceride level of 885 mg/dl or greater?	Yes: Go to #6 Recent TG Level _____ Date _____	No: Pass to RPh. Deny; medical appropriateness
6. Does the patient agree to adhere to a low-fat diet (≤ 20 g of fat per day)?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness
7. Is the request for an FDA-approved indication?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Does the patient have clinically diagnosed severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	Yes: Go to #9 Recent TG Level _____ Date _____	No: Pass to RPh. Deny; medical appropriateness
9. Has the patient failed to have adequate benefit with, or have a contraindication to, an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil)?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria

1. Is there documentation of a positive clinical response (i.e. clinically meaningful reduction in triglyceride level or reduction in episodes of acute pancreatitis)?

Yes: Approve for up to 12 months

No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/26 (MH)

Implementation: TBD

Prior Authorization Criteria Update: Semaglutide (Wegovy®) in Metabolic Dysfunction-Associated Steatohepatitis

Purpose of Update: This update reviews evidence for the use of semaglutide (WEGOVY) in adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 and F3).

Plain Language Summary:

- The Food and Drug Administration recently approved a medicine called semaglutide (WEGOVY) for adult patients who have metabolic dysfunction-associated steatohepatitis without irreversible scarring (cirrhosis) of the liver.¹
- Metabolic dysfunction-associated steatohepatitis is a type of liver disease that is often associated with fat build up in the liver and is not caused by alcohol overuse, viruses, or other conditions that cause liver disease.
- Metabolic dysfunction-associated steatohepatitis is more common in people with other health conditions like obesity, type 2 diabetes, high cholesterol, and high blood pressure. These other conditions are sometimes called metabolic syndrome.
- In people with metabolic dysfunction-associated steatohepatitis who do not have irreversible severe scarring of the liver (e.g., cirrhosis), semaglutide reduced scarring (e.g., fibrosis) and other signs of liver disease in some patients who took this medicine for almost one and a half years (72 weeks).²
- Semaglutide is still being studied to see if it will reduce other serious risks of liver disease such as death and liver failure.²
- Nausea, diarrhea, constipation, and vomiting were the most common side effects of semaglutide.²
- The Drug Use Research and Management group recommends continuing to require prior authorization for semaglutide. Prior authorization means providers must explain why someone needs semaglutide before Medicaid will pay for it.

Conclusions:

- Based on the interim analysis of a single, large, double-blind, placebo-controlled, multicenter RCT, there is moderate quality evidence that semaglutide resolves steatohepatitis without worsening fibrosis (number needed to treat [NNT] = 4) and reduces fibrosis without worsening steatohepatitis (NNT = 7) after 72 weeks of treatment at the weekly 2.4 mg dose of semaglutide.² Part 2 of this RCT will evaluate if cirrhosis free survival is improved over 240 weeks of treatment.² Potential unblinding due to gastrointestinal side effects and uneven attrition between groups already present at 72 weeks may complicate interpretation of longer-term results.

Recommendation:

- Update PA criteria for semaglutide (WEGOVY)

Background

The Oregon Health Plan (OHP) fee for service (FFS) program previously reviewed medications for metabolic dysfunction-associated steatohepatitis (MASH) in August of 2024, including the Food and Drug Administration (FDA) approved agent resmetirom and available phase 2 studies for glucagon-like peptide-1

receptor agonists (GLP1-RA) and dual GLP-1 RA/glucose-dependent insulintropic polypeptides (GIP) agonists.³ Based on review of evidence and compendial designations at that time, a pathway for off-label coverage of MASH was created for semaglutide and liraglutide.³

Semaglutide received an FDA expanded indication for MASH in noncirrhotic adult patients with moderate to advanced liver fibrosis (consistent with stages F2 and F3) in August 2025.¹ Like resmetirom, approval is under the accelerated approval pathway based on improvement of MASH and fibrosis; continued approval is dependent upon verification and description of clinical benefit in confirmatory trials. The evidence supporting this indication was an interim analysis from one ongoing, phase 3, multi-center, randomized, double-blind, placebo-controlled trial (ESSENCE trial; NCT04822181).²

In the ESSENCE trial, adults age 18 years and older with histologically documented steatohepatitis with fibrosis stage F2 or F3, a nonalcoholic fatty liver disease activity score (NAS) of 4 or more (score range 0-8; higher scores indicate greater likelihood of diagnosis) were randomized 2:1 to semaglutide 2.4 mg subcutaneously once-weekly (target dose after 16 week escalation) or placebo.² Randomization was stratified by diabetes comorbidity, fibrosis stage, and geographic region.² Patients were excluded for chronic liver disease unrelated to metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol consumption above predefined thresholds (20 g/d or more in women, 30 g/d or more in men), model for end-stage liver disease (MELD) score of more than 12, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 5 times the upper limit of normal, an estimated glomerular filtration rate of less than 30 mL/min/1.73 m² of body surface area, hemoglobin A1C of more than 9.5%, history of acute pancreatitis, previous GLP1-RA use within 90 days, another MASH medication at an unstable dose, and certain other glucose or lipid or weight lowering medications (other than GLP1-RA) at unstable doses.²

The trial includes 2 parts. Part 1 primary endpoints are resolution of steatohepatitis (NAS of 0 for ballooning and 0-1 for inflammation) with no worsening of liver fibrosis, and a reduction of liver fibrosis (at least one stage; range 0 [no fibrosis] to 4 [cirrhosis]) with no worsening of steatohepatitis (no increase in ballooning, inflammation, or steatosis).² Patients received biopsies at screening and week 72 for the interim results, the first 800 randomized patients were included in this part 1 interim analysis of the total 1197 randomized patients. The primary endpoint for part 2 is cirrhosis-free survival at 240 weeks, to be reported at trial completion. Baseline characteristics appear balanced and key selected characteristics are included in **Table 1**.² Clinical results are in **Table 2**. At the time of interim analysis of the 1197 randomized, 31/802 semaglutide patients (3.9%) and 35/395 placebo patients (8.9%) had withdrawn from the trial.²

Table 1. Key Baseline Characteristics of Patients in ESSENCE Trial²

Characteristic	Semaglutide 2.4 mg weekly N=534	Placebo N=266
Age (mean)	56.3 y	55.4 y
Female	58.6%	54.1%
Race		
-White	26.6%	27.8%
-Asian	67.6%	67.3%
-Black	0.6%	0.8%
Hispanic or Latino	17.8%	19.2%
Body Weight (mean)	95.4 kg	97.6 kg
BMI	34.3	35.0
DM2	55.4%	56.8 %

Fibrosis Stage		
-F2	31.6%	30.5%
-F3	68.4%	69.5%
Abbreviations: BMI = body mass index; DM2 = type 2 diabetes mellitus; mg = milligram; y = year.		

Table 2. Phase 3 Trial Evidence for Use of Semaglutide in Adults with MASH

Study	Comparison	Outcomes	Results	Notes and Limitations
Sanyal AJ, et al. ² (ESSENCE trial) NCT04822181 DB, PC, phase 3, MC, RCT	1. Semaglutide 2.4 mg SC once weekly N=534 vs. 2. Placebo SC once weekly N=266 2:1 randomization All used prefilled pens	<u>Primary Outcome</u> Resolution of steatohepatitis without worsening of liver fibrosis at week 72 <u>Primary Outcome</u> Reduction in liver fibrosis without worsening of steatohepatitis at week 72 <u>Secondary Outcome</u> Weight loss (% change in body weight) at week 72	1. 62.9% 2. 34.3% Difference 28.7% 95% CI (21.1% to 36.2%) P<0.001 NNT 4 1. 36.8% 2. 22.4% Difference 14.4% 95% CI (7.5% to 21.3%) P<0.001 NNT 7 1. -10.5% 2. -2.0% Difference -8.5% 95% CI (-9.6% to -7.4%) P<0.001	-Possible unblinding due to side effects and weight loss with semaglutide -Underrepresentation of Black patients -Geographic representation: Asia 25.1%, Europe 25.3%, North America 35.0%, South American 7.9%, other 6.8% -Histology endpoint data missing for 65/534 (12.2%) semaglutide and 42/266 (15.8%) placebo patients. -Missing data handled by reference-based multiple imputation informed by placebo data. -83.5% semaglutide patients maintained on target dose
Abbreviations: ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; MASH = metabolic dysfunction-associated steatohepatitis; MC = multicenter; NNT = number needed to treat; PC = placebo-controlled; RCT = randomized controlled trial; SC = subcutaneous.				

Adverse events were reported in 86.3% of semaglutide and 79.7% of placebo patients.² Serious events were reported in 13.4% of each group and 2.6% of semaglutide-treated and 3.3% of placebo-treated patients discontinued the study due to side effects.² There were 3 deaths in the semaglutide-treated patients and 6 in the placebo-treated patients.² Nausea, diarrhea, and constipation were the most common side effects and more common in the semaglutide group (Table 3).²

Table 3. Adverse events (full safety set)²

Adverse Event, N (%)	Semaglutide N=800	Placebo N=395
Nausea	290 (36.3)	52 (13.2)
Diarrhea	215 (26.9)	48 (12.2)
Constipation	178 (22.3)	33 (8.4)
Vomiting	149 (18.6)	22 (5.6)
COVID-19	134 (16.8)	74 (18.7)
Decreased appetite	112 (14.0)	11 (2.8)
Abdominal pain	71 (8.9)	32 (8.1)
Fatigue	71 (8.9)	22 (5.6)
Headache	64 (8.0)	26 (6.6)
Abdominal distention	60 (7.5)	14 (3.5)

References:

1. Wegovy (semaglutide) prescribing information. Novo Nordisk Inc. Plainsboro, NJ. Nov 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215256s023lbl.pdf.
2. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *New England Journal of Medicine*. Jun 05 2025;392(21):2089-2099. doi: <https://dx.doi.org/10.1056/NEJMoa2413258>
3. Oregon Health Authority. New Drug Evaluation: Rezdiffra (resmetirom). August 2024. Available at: https://www.orpd.org/durm/meetings/meetingdocs/2024_08_01/archives/2024_08_01_Rezdiffra_NDE.pdf.

Weight Management Drugs

Goal(s):

- To provide guidance for the use of weight management therapies to ensure they are used in the most appropriate patient populations in which evidence supports efficacy and safety.
- Allow case-by-case review for members covered under the EPSDT program. Recommend use of GLP-1 receptor agonists only for FDA-approved indications supported by the evidence.
- To provide guidance for the use of weight management drugs, like semaglutide (WEGOVY) and tirzepatide (ZEPBOUND), to ensure coverage for the most appropriate patient populations in which evidence supports efficacy and safety for reduction in cardiovascular (CV) outcomes, ~~nonalcoholic steatohepatitis (NASH, also called~~ metabolic dysfunction-associated steatohepatitis ~~(MASH)]~~ (previously called nonalcoholic steatohepatitis [NASH]) and obstructive sleep apnea (OSA).

Length of Authorization:

- Up to 6 months
- Renewal up to 12 months

Requires PA:

- All drugs used for weight management.
- Refer to the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist PA Criteria for approval of semaglutide (OZEMPIC and RYBELSUS) and tirzepatide (MOUNJARO) for type 2 diabetes.

Note: Semaglutide is not currently covered for adults who do not have established cardiovascular disease, metabolic dysfunction-associated steatohepatitis (MASH)~~non-alcoholic steatohepatitis (NASH)~~, or type 2 diabetes. Tirzepatide is not currently covered for adults who do not have established obstructive sleep apnea or type 2 diabetes. Liraglutide is not covered for adults who do not have type 2 diabetes or MASH.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Drugs FDA Approved for Weight Management

Drug	Adults	Pediatrics
------	--------	------------

Liraglutide (SAXENDA)	Yes	Yes – 12 years and older
Naltrexone/bupropion (CONTRAVE)	Yes	No
Phentermine/topiramate (QSYMIA)	Yes	Yes – 12 years and older
Semaglutide (WEGOVY)	Yes	Yes – 12 years and older <u>(injection only)</u>
Tirzepatide (ZEPBOUND)	Yes	No
Setmelanotide (IMCIVREE)	Yes	Yes – 2 years and older
Orlistat (Xenical)	Yes	Yes – 12 years and older

Table 2. BMI Cutoffs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (CDC Criteria)

Age (years)	Body mass index (kg/m ²) at 95% percentile	
	Males	Females
12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30

Table 3. Evidence-Supported Indications

Note: Drugs prescribed for only weight management (overweight or obesity) are NOT currently covered

Drug	Indications
Liraglutide	<u>Metabolic dysfunction-associated steatohepatitis (MASH)</u> ~~Non-alcoholic steatohepatitis (NASH)~~ with stage 2 or 3 fibrosis in adults 18 years and older*
Semaglutide	- Established cardiovascular disease (e.g., history of myocardial infarction, stroke, or symptomatic peripheral arterial disease) <u>(tablets or injection)</u> <u>Metabolic dysfunction-associated steatohepatitis (MASH)</u> ~~Non-alcoholic steatohepatitis (NASH)~~ with stage 2 or 3 fibrosis in adults 18 years and older* <u>(injection only)</u>
* <u>MNASH</u> Requirements:	

- Diagnosis by liver biopsy OR all of the following:
 - documentation that the patient does NOT have ongoing or recent (within 2 years) significant alcohol use or chronic or active viral hepatitis. Significant alcohol use can be patient-specific but is typically defined as greater than 21 drinks/week (or >30 g/day) in men and greater than 14 drinks/week (or >20 g/day) in women.
 - provider attestation or documentation that other causes of hepatic steatosis are not suspected based on patient history/presentation or have been ruled out. Examples of other secondary causes of hepatic steatosis include, but are not limited to, Wilson's disease, lipodystrophy, abetalipoproteinemia, medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids).
 - documentation that the patient has, or is receiving drug treatment for, at least 3 of the 5 metabolic risk factors associated with MASH. Risk factors include:
 - Overweight or obesity or increased waist circumference (BMI $\geq$ 25 kg/m² or ethnicity adjusted equivalent)
 - Hypertension
 - Type 2 diabetes mellitus
 - Hypertriglyceridemia
 - Decreased level of high density lipoprotein (HDL)
- fibrosis stage 2 or 3 as shown by appropriate diagnostic test within past 24 months [appropriate tests may include biopsy, vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE), enhanced liver fibrosis test (ELF)]
- medication being ordered by, or in consultation with, a hepatologist or gastroenterologist

Tirzepatide

- Moderate to severe obstructive sleep apnea (OSA) in adults with obesity

Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy after an initial approval by FFS?	Yes: Go to Renewal Criteria	No: Go to #3
3. <u>Is the requested indication MASH AND does patient meet all components of Table 3?</u>	<u>Yes: Go to #14</u>	<u>No: Go to #4</u>

Approval Criteria		
4. Does the patient have a BMI corresponding to one of the following: 1) ≥ 30 kg/m² or 2) ≥ 25 kg/m² and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, fatty liver disease, or cardiovascular disease] or 3) a BMI at the 95th percentile or greater for age and sex (Table 2 above)?	Yes: Go to #<u>54</u> Record baseline BMI	No: Deny; medical appropriateness
5. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy? See clinical notes below	Yes: Go to #<u>65</u>	No: Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.
6. Is the member eligible for EPSDT review AND is the requested medication FDA-approved for their age (Table 1)?	Yes: Go to #<u>76</u>	No: Go to #<u>124</u>
7. Is the request for setmelanotide?	Yes: Go to #<u>87</u>	No: Go to #<u>109</u>
8. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR does the patient have Bardet—Biedl syndrome (BBS)?	Yes: Go to #<u>98</u>	No: Deny; medical appropriateness.

Approval Criteria		
9. Does the patient have a history of depression and/or suicidal ideation?	Yes: Deny; medical appropriateness.	No: Approve for up to 6 months.
10. Does the patient have comorbidities (e.g., hypertension, dyslipidemia, diabetes, fatty liver disease, depression, or sleep apnea)?	Yes: Approve for 6 months	No: Go to #1 ~~0~~
11. Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6-month timeframe*? * See Clinical Notes Below	Yes: Approve for 6 months.	No: Deny; medical appropriateness. Lifestyle modifications are recommended by guidelines.
12. Is the request for an indication <u>meeting all components of</u> ~~in~~ Table 3? Note: drugs ~~when~~ -prescribed for weight management (e.g., obesity or overweight) in the absence of another evidence-supported indication are not currently covered.	Yes: Go to #1 ~~3~~ ²	No: Pass to RPh. Deny; drugs are not covered by OHP for adults when indicated for weight loss.
13. Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6-month timeframe?	Yes: Go to #1 ~~3~~	No: Deny; medical appropriateness

Approval Criteria		
14. Is there documentation of a type 2 diabetes diagnosis?	Yes: Go to #1 ~~6~~ <u>5</u>	No: Go to #1 ~~5~~ <u>4</u>
15. Has the patient been screened for diabetes within the past year and do screening results indicate they do not have diabetes (e.g., HbA1c <6.5% or fasting blood glucose <126 mg/dl (7 mmol/L)?	Yes: Go to #1 ~~6~~ <u>5</u>	No: Pass to RPh; Deny; medical appropriateness. Recommend screening and if positive recommend a GLP-1 RA indicated for glucose lowering (see GLP-1 RA/GIP RA PA criteria)
16. Is the request for tirzepatide (ZEPBOUND)?	Yes: Go to # ~~20~~ <u>19</u>	No: Go to #1 ~~7~~ <u>6</u>
17. Is the request for semaglutide (WEGOVY)?	Yes: Go to #1 ~~8~~ <u>7</u>	No: Approve for up to 6 months
18. Is the patient currently taking semaglutide (OZEMPIC) 2.0 mg weekly and is able to tolerate the medication and is still desiring additional weight loss?	Yes: Approve for up to 6 months	No: Go to #1 ~~9~~ <u>8</u>
19. Will the patient try semaglutide (OZEMPIC) for at least 4 months to ensure tolerability/compliance?	Yes: Approve Ozempic for up to 6 months * Load PA for OZEMPIC	No: Pass to RPh. Deny; medical appropriateness.
20. Does the patient have obesity (BMI of 30 kg/m ² or greater) and moderate to severe obstructive sleep apnea (OSA)? - Moderate OSA is defined as an apnea-hypopnea index (AHI) of 15 events/hour or more - Severe OSA is defined as an AHI of 30 events/hour or more	Yes: Approve tirzepatide (ZEPBOUND) for up to 6 months	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is this a request for continuation of therapy with a weight loss medication previously approved by FFS?	Yes: Go to #2	No: Go to Approval Criteria above
<u>2.</u> Is the requested indication MASH?	<u>Yes: Go to #9</u>	<u>No: Go to #3</u>
<u>2.3.</u> Is the person requesting the medication less than 18 years of age?	Yes: Go to # <u>34</u>	No: Go to # <u>45</u>
<u>3.4.</u> Has the patient lost at least 1% of BMI from baseline or maintained at least a 1% BMI weight loss?	Yes: Go to # <u>78</u>	No: Deny; medical appropriateness
<u>4.5.</u> Is the request for ongoing treatment for someone with established cardiovascular disease (e.g., history of myocardial infarction, stroke, or symptomatic peripheral arterial disease), ~~NASH~~ or OSA?	Yes: Go to # <u>56</u>	No: If not eligible for EPSDT review: Pass to RPh. Deny; drugs are not covered by OHP for adults when indicated for weight loss. If eligible for EPSDT review: Go to #5
<u>5.6.</u> Has the patient lost or maintained a BMI reduction of 5% or more?	Yes: Go to # <u>67</u>	No: Deny; medical appropriateness
<u>6.7.</u> Has the patient been adherent to therapy based on provider attestation?	Yes: Go to # <u>78</u>	No: Deny; medical appropriateness

Renewal Criteria		
<u>7-8.</u> Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet)?	Yes: Approve for up to 12 months.	No: Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise.
<u>9.</u> Does the provider attest that the patient has been adherent to therapy OR is adherence apparent from medication claims history?	Yes: Go to #10	No: Pass to RPh. Approve once, for 3 months. <u>Request documentation of adherence.</u>
<u>10.</u> Has the patient had a complete metabolic panel, liver enzymes, or other appropriate biochemical or noninvasive imaging test within the past 12 months to assess for potential disease progression? <u>Additional example tests: fibrosis-4 index (FIB-4), enhanced liver fibrosis test (ELF), vibration controlled transient elastography (VCTE), magnetic resonance elastography (MRE)</u>	Yes: Go to #11	No: Pass to RPh. Approve once, for 3 months. <u>-Recommend biochemical monitoring.</u>
<u>11.</u> If semaglutide initiation was more than 3 years ago, has the patient had noninvasive imaging (e.g., VCTE or MRE) or repeat liver biopsy to assess for progression of fibrosis in the past 3 years? <u>If not applicable because semaglutide started less than 3 years ago skip to question #12</u>	Yes: Go to #12	No: Pass to RPh. Approve once, for 3 months. <u>Recommend noninvasive imaging or repeat biopsy.</u>

Renewal Criteria		
<u>12. Does the patient have evidence of stage F4 fibrosis (cirrhosis) OR has fibrosis stage worsened (e.g., stage F2 to F3) since starting semaglutide?</u>	<u>Yes: Pass to RPh. Deny: medical appropriateness</u>	<u>No: Go to #13</u>
<u>13. Is there documentation of a risk/benefit assessment for ongoing treatment with semaglutide with possible resolution of metabolic comorbidities?</u>	<u>Yes: Approve for 12 months</u>	<u>No: Pass to RPh. Approve once, for 3 months.</u> <u>Recommend provide additional documentation.</u>

*Clinical Notes

Adapted from the following guideline on the treatment of adolescents with obesity:	
American Academy of Pediatrics. <i>Pediatrics</i>. 2023;151(2): e2022060640. Available at: https://publications.aap.org/pediatrics/article/151/2/e2022060640/190443/Clinical-Practice-Guideline-for-the-Evaluation-and?autologincheck=redirected	
Recommended Behavior Strategies	
Strategy	Description
1. Reduction in sugar-sweetened beverages (SSBs)	Higher intake of sugar-sweetened beverages (carbonated beverages, sweetened beverages, soda, sports drinks, and fruit drinks) is associated with greater weight gain in adults and children. The American Heart Association (AHA) recommends not more than 25 g (6 tsp) each day of added sugar and not more than 1, 8-oz serving of SSB per week. The AAP discourages the consumption of sports drinks and energy drinks for children and adolescents. The AAP statement on fruit juice notes that it is a poor substitute for whole fruit because of its high sugar and calorie content and pediatricians should advocate for elimination of fruit juice in children with excessive weight gain.
2. Choose My Plate	MyPlate is the US Department of Agriculture's (USDA) broad set of recommendations for healthy eating for Americans. These recommendations include multiple healthy diet goals: low in added sugar, low in concentrated fat, nutrient dense but not calorie dense, within an appropriate calorie range without defined calorie restriction, and with balanced protein and carbohydrate. The principles can be adapted to different food cultures. There is a surprising dearth of literature on the impact of these guidelines on health and BMI outcomes and on the most effective education practices. Available at: USDA choose my plate.gov

3. 60 minutes daily of moderate to vigorous physical activity	Aerobic exercise, especially for 60 min at a time, is associated with improved body weight in youth although its effect may be small and variable. It is also associated with better glucose metabolism profiles. High-intensity interval training in youth with obesity may improve body fat, weight, and cardiometabolic risk factors, although the effect is variable. The Physical Activity Guidelines for Americans recommends 60 min per day for children and adolescents.
4. Reduction in sedentary behavior	Reduction in sedentary behavior, generally defined as reduced screen time, has consistently shown improvement in BMI measures, although impact is small. Early studies focused on reduced television, a discrete activity that is simpler than current multifunctional electronic devices. The AAP recommends no media use under age 18 month, a 1-hour limit for ages 2–5 years, and a parent- monitored plan for media use in older children, with a goal of appropriate, not- excessive use but without a defined upper limit.
The activities most commonly associated with positive behavior change are: parental involvement in goal setting, problem solving, social support, demonstrating desired behaviors, and home environment modifications to support positive change.	
Abbreviations: AAP – American Academy of Pediatrics; BMI = body mass index; oz = ounce; tsp = teaspoon; USDA = United States Department of Agriculture	

P&T/DUR Review: 2/26 (SF); 4/25 (KS); 8/24 (SS/SF); 6/24 (KS)
Implementation: TBD; 5/12/25; 9/1/24; 7/1/24



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Drug Class Update: Sedatives

Date of Review: February 2026

Date of Last Review: April 2023 (circadian rhythm disorders)
August 2022 (insomnia)

Dates of Literature Search: 09/01/2022 - 11/21/2025

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this update is to review recent evidence for the use of sedatives in the treatment of chronic insomnia disorder.

Plain Language Summary:

- Is there any new evidence that would change the current policy for medicines to treat a person's ability to fall asleep and/or stay asleep?
- Insomnia is the inability to fall asleep, stay asleep, or achieve quality sleep.
- CBT-I is a sleep management method that involves a combination of thinking and behavior techniques such as control of surroundings, limiting sleep to only certain times, relaxation methods, and good sleep practices.
- A 2025 evidence review concluded that it is uncertain whether a specific type of medicines called dual orexin receptor antagonists (DORAs) are equal or better than other medicines for insomnia.
- The Veterans Administration/Department of Defense (VA/DoD) strongly recommends cognitive behavioral therapy for insomnia (CBT-I) for chronic insomnia. CBT-I is a non-medical program that helps people change habits and thoughts that make it hard to sleep.
- In 2024, the Oregon Mental Health Clinical Advisory Group (MHCAG) recommended cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for all patients with sleep disorders before using medicine. When medicine is necessary, patients should not take it for more than 4 weeks whenever possible. MHCAG recommends providers prescribe a type of medicine called benzodiazepines only as needed for 7-10 days, and prescribers should have a plan for tapering (or gradually stopping the medicine).
- Certain types of medicines may be helpful for specific sleep symptoms including:
 - non-benzodiazepine hypnotics [zolpidem, eszopiclone] for getting to sleep and/or staying asleep,
 - dual orexin receptor antagonists (DORAs) [suvorexant, lemborexant] or antidepressants [doxepin, trazodone] for staying asleep, and
 - benzodiazepines [temazepam, triazolam] for severe sleep problems linked to anxiety.
- Providers must explain to the Oregon Health Authority why someone needs a sedative before Medicaid will pay for it. This process is called prior authorization.

- Providers must document that the patient has tried CBT-I. Use of a sedative beyond 30 days requires documented improvement in sleep, function or quality of life, and evaluation of long-term side effects.

Research Questions:

1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders?
2. Are sedatives more effective or associated with more harms than no treatment when used to treat sleep disorders?
3. Are there subgroups of patients based on specific demographics, co-morbidities or other factors (e.g., age, co-morbid behavioral or mental disorders, concomitant medications, etc.) in which one sedative is more effective or associated with fewer adverse events than another sedative?

Conclusions:

- Based on evidence reviewed in a 2025 DERP report, there is uncertainty if dual orexin receptor antagonists (DORAs) are equally effective or more effective than other medications for insomnia.¹ Four studies evaluated daridorexant (n=1), lemborexant (n=2), and suvorexant (n=1) compared to alternative therapy.¹
 - It is unclear whether daridorexant is more or less effective than zolpidem (moderate quality of evidence; 1 randomized controlled trial [RCT]).¹
 - There is insufficient evidence on the effectiveness of either lemborexant compared with flurazepam or suvorexant compared with zolpidem for insomnia.¹
 - Lemborexant may be associated with greater improvements in sleep compared with zolpidem; however, the differences are small and may not be clinically meaningful (low quality of evidence; 1 RCT).¹
 - DORAs have overall similar or lower rates of adverse events compared to flurazepam, zolpidem, and eszopiclone.¹
- In individuals with Alzheimer's disease (AD), sedative-hypnotics reduced wakefulness after sleep onset compared to placebo but were also associated with safety concerns such as potential for mental confusion, hallucinations, and agitation.² Sleep efficiency and total sleep time were improved with eszopiclone and DORA treatment.² Although sleep latency slightly improved with eszopiclone compared to placebo, REM latency also increased. Melatonin showed no significant benefit over placebo for sleep efficiency or total sleep time.²
- In 2025, the VA/DoD issued the following recommendations for adult patients with chronic insomnia:³
 - Behavioral Therapy Recommendations (e.g., CBT-I and Brief behavioral treatment for insomnia [BBT-I])
 - FOR CBT-I treatment (Strong recommendation; moderate-quality evidence)
 - FOR BBT-I treatment (Weak recommendation; moderate-quality evidence)
 - AGAINST sleep hygiene education as a stand-alone treatment (Weak recommendation; low-quality evidence)
 - Pharmacotherapy Recommendations (if offered by provider)
 - FOR CBT-I over pharmacotherapy as first-line treatment for chronic insomnia (Weak recommendation; low-quality evidence)
 - FOR use of daridorexant, lemborexant, suvorexant, doxepin, eszopiclone, zaleplon, or zolpidem (Weak recommendation; low-quality evidence)
 - AGAINST use of antipsychotic drugs, benzodiazepines, diphenhydramine, or trazodone (Weak recommendation; very low-quality evidence)
 - NEITHER FOR NOR AGAINST use of ramelteon (No recommendation; very low-quality evidence)
- In 2024, the MHCAG updated recommendations for management of chronic insomnia.⁴
 - Use an evidence-based approach.
 - Offer CBT-I to all patients as the initial treatment for chronic insomnia.

- CBT-I provides clinically meaningful long-term improvement in critical outcomes of remission, response, sleep onset latency (SOL), wake after sleep onset (WASO), and sleep quality (moderate-quality evidence).
- CBT-I treatment is usually 6 sessions, which can be provided in-person or via telemedicine. A minimum of 4 sessions is needed for treatment response.
- Use shared decision-making when adding pharmacologic therapies: Discuss benefits, risks, costs, and patient preferences before prescribing medications.
 - Reserve short-term pharmacotherapy for patients who cannot access CBT-I, who have persistent symptoms despite CBT-I, or who need temporary relief.
- Use medications if necessary for limited duration (<4 weeks)
 - Non-benzodiazepine hypnotics (zolpidem, eszopiclone) for sleep onset and/or sleep maintenance.
 - Consider orexin receptor antagonists (suvorexant, lemborexant) or antidepressants (doxepin, trazodone) for sleep maintenance.
 - Benzodiazepines (temazepam, triazolam) may be considered for severe insomnia with anxiety; use as needed for 7-10 days and plan for tapering; discouraged for long-term use.
- Reassess medication efficacy and adverse effects within 2-4 weeks of initiation.
 - Avoid use of medications in patients with significant respiratory, hepatic, or renal impairment, or those with increased fall risk.
 - Taper medications to minimize rebound insomnia and withdrawal.
- Special Populations
 - Older adults: prioritize non-pharmacologic strategies; use lower doses and shorter durations if medications are needed.
 - Comorbid psychiatric or medical conditions: tailor therapy to address both insomnia and the underlying disorder.

Recommendations:

- Remove PA for preferred products when there is no history of an opioid or sedative agent for short term use (4 weeks).
- Designate one sedative agent that is not from the benzodiazepine or GABA-A receptor agonist class as preferred on the preferred drug list (PDL).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Insomnia

- CBT-I is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine and the European Sleep Research Society based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.⁵ Long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects (e.g., fractures, dementia) based on low-quality evidence.⁵
- FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.⁵
- There is insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.⁵ Resources describing best practices for benzodiazepine tapers have been published by the MHCAG.

- In elderly patients over 65 years of age, there is evidence supporting use of eszopiclone to improve total sleep time and wake time after sleep onset, use of zolpidem and ramelteon to improve sleep onset latency, and doxepin to improve insomnia symptoms.⁵
- In patients with sleep disturbances and dementia, there is low quality evidence that short-term (2 weeks) treatment with trazodone may improve sleep efficiency and total sleep time.⁶
- Melatonin did not demonstrate any change in sleep outcomes in adults based on low quality evidence.⁶

Circadian Rhythm Sleep-Wake Disorders

- There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
- Melatonin or a melatonin agonist may be an option for adults, adolescents, and children with delayed sleep-wake phase disorder (low to moderate quality evidence), and in children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder (moderate quality evidence).⁷

Current Policy

- Prior authorization is currently required for all sedative medications except for melatonin in patients less than or equal to 18 years of age.
- Insomnia is funded when paired with CBT. Short term (up to 1 month per year) treatment with sedative-hypnotic medications is funded if the patient is currently in CBT or has failed to respond to recent CBT (in the past year). Long-term (more than 1 month) treatment of insomnia with sedative-hypnotic medications is not currently funded.
- All drugs currently require prior authorization (PA) for this class except melatonin in children.⁵⁻⁷

Background:

Insomnia is the most common of type sleep disorder identified by the American Academy of Sleep Medicine's (AASM) International Classification of Sleep Disorders, Third Edition (ICSD-3).⁸ Other frequently observed conditions that affect sleep include central disorders of hypersomnolence, sleep-related breathing disorders, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.^{8,9} The current review will emphasize medications listed in the Sedative PDL class (see **Appendix 1**) for treatment of insomnia. Drugs that are sometimes used for sleep but not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants, and atypical antipsychotics. Many of these medications are covered in other class reviews and are addressed through different PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine when prescribed specifically for insomnia.

Insomnia is the inability to fall asleep, stay asleep, or achieve quality sleep.^{10,11} Insomnia may be classified by duration (e.g., short-term or chronic) and by type of sleep disturbance. People with insomnia may have trouble with sleep initiation, maintenance of sleep, or with premature awakening which can cause concentration or memory issues, reduced productivity, cause mood fluctuations, and contribute to fatigue during hours of wakefulness.¹² Up to 20% of people are affected by intermittent short-term insomnia (typically < 3 months), and roughly 10% experience chronic insomnia (symptoms for ≥ 3 months that occur ≥ 3 times weekly) with symptoms severe enough to affect daily function.^{11,13,14} Older individuals tend to experience insomnia at higher rates than the general population, and insomnia is more common in women than men.^{15,16} Other risk factors that may predispose an individual to develop insomnia include shift work, lower socioeconomic status, family history of insomnia, and genetic factors.¹⁷ Insomnia may occur either independently or as a result of other medical and psychiatric conditions.¹⁵ Chronic insomnia symptoms have been associated with metabolic complications, cognitive impairment, depression and psychiatric issues that can result in a reduced health-related quality of life (HRQoL) especially in patients over 65 years of age.^{13,18} Insomnia can also worsen outcomes for patients with comorbid illness such as post-traumatic stress disorder and cardiovascular disease.^{10,18-20} Therefore, prompt identification and treatment of contributing factors is important for the effective management of insomnia symptoms.

Insomnia etiology and pathology is not fully understood but likely involves a complex interplay of genetic, psychophysiological, behavioral, and biochemical interactions.^{15,21,22-28} Treatment goals for insomnia are to improve the quality and quantity of sleep and to reduce associated daytime impairments.²⁹ Once comorbidities and other contributing factors that interfere with sleep quality have been addressed, nonpharmacologic interventions such as CBT-I are recommended as standard first-line therapy for chronic insomnia.^{12,13,30-33} CBT-I is a multi-faceted sleep management strategy that involves a combination of psychological and behavioral techniques such as stimulus control, sleep restriction, relaxation therapy, and sleep hygiene (**See Table 1**).^{13,35} Both brief and longer CBT-I interventions are recommended by the AASM guidelines.³⁰ If CBT-I is not effective or not available, a sedative can be offered but combination therapy has not demonstrated additional benefits or harms compared to CBT-I alone.^{11,31} CBT-I has internet-based offerings that have demonstrated outcomes equally efficacious as face-to-face CBT-I and may be a viable alternative for patients with provider access challenges.^{35,36}

Table 1. Key Components of Cognitive Behavioral Therapy for Insomnia (modified)³⁴

Method	Goals	How Accomplished
Stimulus Control	Strengthen association between bed/bedroom and sleep; produce a consistent sleep schedule	-Minimize napping -Go to bed only when sleepy -Get out of bed if unable to sleep -Use the bed/bedroom only for sleep and intimacy -Wake up at the same time each day
Sleep Restriction	Increase homeostatic drive for sleep to improve sleep quality	-Reduce time in bed to the actual sleep duration (based on sleep diaries) -Time in bed is then gradually increased until the individual achieves an optimal sleep duration
Relaxation Training	Reduce tension and intrusive thoughts which interfere with the ability to sleep	-Deep breathing exercises -Progressive muscle relaxation -Biofeedback -Guided imagery
Cognitive Restructuring	Reduce worry and change misconceptions associated with sleep and insomnia	-Use Socratic questioning to challenge inaccurate patterns of thinking regarding the effect of sleep on patient's life
Sleep Hygiene Education	Provides guidelines about factors that may help or interfere with sleep	-Do not eat a heavy meal or drink alcohol within two hours of bedtime -Limit caffeine intake after lunchtime -Exercising regularly but not within 2 hours of bedtime -Keep the bedroom quiet, dark and at a cool, comfortable temperature

Medications may be used for short-term (<4 weeks) treatment of insomnia due to their rapid onset, however, the safety and efficacy of long-term use is limited due to tolerance, the potential for dependence, and dangerous withdrawal symptoms upon discontinuation.^{11,13} DORAs (e.g. suvorexant, lemborexant, daridorexant) are indicated for sleep maintenance or to improve sleep onset.¹³ Certain benzodiazepines (such as triazolam and temazepam) have sleep indications, but are usually prescribed very short-term (<10 days) due to an extensive adverse effect profile.^{11,13} The benzodiazepine receptor agonists (BzRAa) eszopiclone and zolpidem have indications to treat sleep onset and sleep maintenance while zaleplon is only indicated for the treatment of sleep onset insomnia.^{11,13} Heterocyclic antidepressants such as the histamine receptor antagonist doxepin and the melatonin receptor agonist ramelteon also have indications to treat insomnia.^{11,13} A summary of recommended therapies by the AASM may be found in **Table 2**. The newer DORAs, lemborexant and

daridorexant, were FDA approved after the AASM guidelines were published but clinical trials support their efficacy for sleep-onset and sleep-maintenance symptoms.¹³

Table 2. Sedative Therapies and Recommendations by the American Academy of Sleep Medicine (Modified)¹²

Sedative Class	Treatment	AASM Recommendation	Quality of Evidence	AASM Benefits vs. Harm Assessment
Benzodiazepine (GABA-A) receptor agonists	Eszopiclone (2–3 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
	Zaleplon (10 mg)	Option for sleep-onset insomnia (versus no treatment)	Low	Benefits outweigh harm
	Zolpidem (10 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Very Low	Benefits outweigh harm
Orexin (hypocretin) receptor antagonist	Suvorexant (10–20 mg)	Option for sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
Benzodiazepines	Temazepam (15 mg)	Option for sleep-onset & sleep-maintenance insomnia (versus no treatment)	Moderate	Benefits outweigh harm
	Triazolam (0.25 mg)	Option for sleep-onset insomnia (versus no treatment)	High	Benefits ≈ harm
Melatonin agonist	Ramelteon (8 mg)	Option for sleep-onset insomnia (versus no treatment)	Very Low	Benefits outweigh harm
Heterocyclics	Doxepin (3–6 mg)	Option for sleep-maintenance insomnia (versus no treatment)	Low	Benefits outweigh harm
	Trazodone (50 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Moderate	Harm outweighs benefits
Anticonvulsant	Tiagabine (4 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Very Low	Harm outweighs benefits
Over-the-counter preparations	Diphenhydramine (50 mg)	Not suggested for sleep-onset or sleep-maintenance insomnia	Low	Benefits ≈ harm
	Valerian (varied doses)		Low	Benefits ≈ harm
	Melatonin (varied doses)		Low	Benefits ≈ harm
	L-tryptophan		Low	Harm outweighs benefits

Abbreviations: GABA-A = Gamma-aminobutyric acid-A

Long-term treatment of chronic insomnia with a sedative (≥12 weeks) is not recommended because of lack of evidence and increased risk of adverse effects based on low-quality evidence.¹¹ Most sedative drugs indicated for insomnia contain FDA labeling recommendations to re-evaluate comorbid diagnoses which could be contributing to symptoms if insomnia persists for more than 7-10 days of treatment.¹³ In general sedating antidepressants (e.g., trazodone) and antihistamines (e.g. diphenhydramine) are not generally recommended due to lack of efficacy and increased risk of adverse effects.¹¹ Melatonin is not recommended as a treatment to improve sleep onset or sleep maintenance due to insufficient evidence of benefit.¹¹

Sedative medications may cause dizziness, daytime drowsiness, respiratory depression, and somnolence.³⁷⁻⁴⁵ Long-term sedative use may be associated with increased risk of fractures and dementia based on evidence from observational studies.^{3,46,47} The fracture risk appeared to correlate with the length of use, with new users of these drugs at greatest risk of hip fracture.^{3,46,47} Non-benzodiazepine sedatives include FDA warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors

(such as sleep driving), depression, and suicidal thoughts and actions.³⁹⁻⁴⁵ Women or elderly who metabolize and eliminate sedative medications more slowly from the body may be at higher risk for daytime impairment.^{39,40} The FDA warns that a sedative can result in next-day impaired function even if patients feel fully awake.^{39,40} Benzodiazepine sedatives are also associated with physical dependence; therefore, taper plans are used to minimize withdrawal symptoms and facilitate safe discontinuation after routine, extended use.³ Although non-benzodiazepine sedatives do not carry a boxed warning for dependence, abrupt discontinuation may still produce troublesome adverse effects such as nausea, sweating, tremors, and seizures.^{39-45,48,49} Provider resources and best practices for benzodiazepine tapers were recently published by the Oregon Health Authority MHCAG.⁵⁰ Taper schedules should be individualized based on patient circumstances, diagnoses, dose, and length of benzodiazepine use.⁴⁹ Many patients may benefit in switching, or cross-tapering, to a longer-acting benzodiazepine like diazepam before reducing their total benzodiazepine dose.⁵⁰ For the majority of sedative agents, such as benzodiazepines, BzRAs, and sedating antidepressants, a gradual reduction of 5-10% of the current daily dose every 1 to 2 weeks has been recommended by multiple major guidelines as safe and reasonable initial taper strategy.^{30,48} Due to the potential for withdrawal, patients on low-dose use of benzodiazepines may find benefit from a 20% weekly reduction.⁴⁹ Patients on higher doses of benzodiazepines will likely require a longer taper period such as 2 to 6 months (or longer in unique cases).⁴⁹ A common taper strategy for patients on high doses of benzodiazepines is a weekly dose reduction of 25% over 2 weeks until 50% of the dose remains then further reduce the dose by 1/8 (~12%) every week.⁴⁹ Due to the potential for withdrawal symptoms with rapid dose reduction, periodic monitoring is recommended with adjustments to slow down the taper plan if needed.⁴⁹ Tapering of DORAs and melatonin/melatonin receptor agonists are generally not recommended.⁵¹⁻⁵⁴ The Oregon Health Plan typically requires PA and engagement in a CBT-I program before a prescription claim for a sedative is approved. Use of a sedative beyond 30 days requires documentation of improvement in symptoms, function or quality of life, and a provider discussion with the patient about the long-term effects of ongoing medication use.⁴

Although polysomnography is the gold standard for objective sleep assessment, it is not required for diagnosis of chronic insomnia due to an inconsistent correlation with clinical symptoms.¹² Therefore, patient surveys, sleep logs, or actigraphy are often used to assess symptoms, functioning, and health-related quality of life (HRQoL).⁵⁵⁻⁵⁸ However, efficacy differences among sedatives are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy.⁵⁹ Some studies of sedatives for primary insomnia have reported that almost two-thirds of the drug response could be also be observed in the placebo group.⁵⁹ Common outcomes for sleep interventions in clinical trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Clinically meaningful improvement has been proposed by the AASM (**Table 3**).¹¹ Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.⁶⁰

Table 3. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).¹¹

Outcome (units)	Description	Minimum Clinically Important Difference Versus Placebo**		
		Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	Time elapsed from getting into bed to falling asleep	10	10	20
Total Sleep Time (min)	Represents the total sleep duration during a 24-hour period.	20	20	30
Wake After Sleep Onset (min)	Duration of time spent awake after the onset of sleep.	20	20	30
Sleep Efficiency (%)	Percentage representing the proportion of time spent asleep while in bed.	5	5	10
Number of Awakenings (n)	Expressed as the total count of awakenings during nighttime sleep.	2	2	0.5
Quality of Sleep (varies***)	Satisfaction of sleep experience	Varies	Varies	Varies

**Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.

***For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significant.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

After review, 33 systematic reviews were excluded due to poor quality (e.g, indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Drug Effectiveness Review Project (DERP): Dual Orexin Receptor Antagonists (DORAs) for Insomnia¹

A 2025 DERP systematic review evaluated DORAs for the treatment of insomnia.¹ The review included RCTs published through February 24, 2025. Clinical outcomes of interest included WASO, latency to persistent sleep (LPS), total sleep time (TST), sleep quality, fatigue, alertness, and safety/adverse events (AEs).¹ The review identified 4 studies comparing daridorexant (n=1), lemborexant (n=2), and suvorexant (n=1) to an alternative therapy.¹ Evidence was graded as moderate (1 study), low (2 studies), or very low (1 study) quality reflecting substantial uncertainty in the estimate of treatment effects.¹ The evidence summary for each of the trials is presented in **Table 4**.

Table 4. DERP Evidence Summary Dual Orexin Receptor Antagonists (DORAs) for Insomnia¹

Comparisons	Number of Studies; Participants	Outcomes Assessed	Quality of Evidence	Rationale
Daridorexant vs. Zolpidem	1 RCT (N = 299)	TST, WASO, LPS, Safety	Moderate	Downgraded 1 level for imprecision (i.e., not assessable)
Lemborexant vs. Flurazepam	1 RCT (N = 69)	Safety	Low	Downgraded 1 level for imprecision and 1 level for indirectness (i.e., only single dose administered)
Lemborexant vs. Zolpidem	1 RCT (N=798)	WASO, LPS, Safety	Low	Downgraded 1 level for risk of bias and 1 level for indirectness (i.e., only people aged 55 and older were included)
Suvorexant vs. Eszopiclone	1 RCT (N – 18)	Safety	Very low	Downgraded 1 level for risk of bias, 1 level for indirectness (i.e., specific population) and 2 levels for imprecision (i.e., very small sample size)

Abbreviations: DERP = drug effectiveness review project; LPS = latency to persistent sleep; RCT = randomized controlled trial; TST = total sleep time; WASO = wake after sleep onset.

The findings for each outcome of interest may be summarized as follows:

- Total sleep time (TST):
 - In the trial evaluating daridorexant versus zolpidem, TST was increased in both groups; only higher daridorexant doses (10 mg, 25 mg, 50 mg) achieved the TST MCID of 55 minutes; it was unclear if there are any significant differences between both agents.¹
- Wake after sleep onset (WASO):
 - In the trial of daridorexant versus zolpidem, WASO was reduced from baseline in a dose-dependent fashion for both groups at weeks 2 and 4; it was unclear if there are any significant differences between both agents.¹
 - In the trial of lemborexant versus zolpidem, lemborexant had statistically significant improvements in WASO compared with zolpidem, but differences between groups were less than the MCID threshold of 20 minutes and, therefore, may not be clinically meaningful.¹
- Latency to persistent sleep (LPS):
 - In the trial of daridorexant versus zolpidem, LPS was reduced in both groups, but it was unclear if there are any significant differences between both agents.¹
 - In the trial of lemborexant versus zolpidem, lemborexant demonstrated statistically significant reductions in LPS, but differences between groups were less than the MCID threshold of 15 minutes and, therefore, may not be clinically meaningful.¹
- Insomnia severity index (ISI):
 - In the trial of daridorexant versus zolpidem, improvements in the insomnia severity index (ISI) were observed across both groups compared to baseline; the MCID of 6 points was met for both groups at day 30.¹
- Adverse events (AEs):
 - In the trial of daridorexant versus zolpidem, roughly one-third of people experienced an AE but serious AEs were rare; the most common AEs in both groups were headache (around 8% to 10%) and somnolence (around 5% to 7%); upper abdominal pain, dizziness, fatigue, nasopharyngitis, and nausea were also reported in the zolpidem group (around 7% to 8%).¹
 - In the trial of lemborexant versus flurazepam, both groups experienced treatment-emergent AE, but no serious AEs were observed; the most common AEs in both groups was somnolence (1.4% in the lemborexant 5 mg group, 4.4% in the lemborexant 10 mg group, and 2.9% in the flurazepam group).¹
 - In the trial of lemborexant versus zolpidem, both groups experienced treatment-emergent AEs (lemborexant: 28% to 31%; zolpidem: 36%); the most common AEs in both groups was headache (lemborexant: 5% to 7%; zolpidem: 5%).¹ Serious AEs and severe AEs were around 1% or less for both groups.¹
 - In the trial of suvorexant versus eszopiclone, both groups experienced treatment-emergent AEs. The most common AE in the suvorexant group was fatigue (89%) and in the eszopiclone group was somnolence (67%); no serious AEs were observed in either group.¹

Pharmacological Interventions to Improve Sleep In People With Alzheimer's Disease: A Meta-Analysis Of Randomized Controlled Trials²

A 2024 systematic review and meta-analysis evaluated the efficacy and safety of pharmacological interventions for improving sleep in individuals with Alzheimer's disease (AD).² Literature was searched from January 2000 to July 2023.² The evidence for pharmacological treatments included 14 studies with trial sizes that ranged from 20 to 285 participants.² Placebo-controlled interventions included the following agents from the sedatives class: zopiclone (not available in United States - 1 study), zolpidem (1 study), eszopiclone (1 study), lemborexant (1 study), suvorexant (1 study), trazodone (2 studies), and melatonin (6

studies).² Twenty-nine sleep outcomes were analyzed via meta-analysis with sleep efficiency and daytime total sleep time as the most frequently assessed sleep outcomes.² Six of the 14 studies were graded as having low risk of bias while the remaining 8 studies had unclear risk of bias.² The review found that overall, sedative-hypnotics reduced wakefulness after sleep onset but also carry safety concerns such as potential for mental confusion, hallucinations, and agitation.² Sleep efficiency and total sleep time improved significantly with eszopiclone and DORAs.² Although sleep latency slightly improved with eszopiclone, undesirable rapid eye movement (REM) latency also increased.² Melatonin showed no significant benefit over placebo.² Outcomes of key sleep measures are summarized in **Table 5**.

Table 5. Pharmacological interventions to improve sleep in people with Alzheimer’s disease.²

Outcome	Drug Therapy vs. Placebo Weighted Mean Difference (WMD)	Effects by Drug Class or Drug vs. Placebo
Sleep Efficiency (%)	WMD = 0.32 (95% CI 0.02 to 0.62)	• Eszopiclone: WMD 0.94 (95% CI 0.52 to 1.36); • Orexin antagonists: WMD 0.33 (95% CI 0.13 to 0.53)
Total Sleep Time (TST) - mins	WMD = 15.77 min (95% CI 2.88 to 28.65)	• Orexin antagonists: WMD +28 min (95% CI: 9.70, 46.30); • Eszopiclone: WMD +10 min (95% CI –3.65 to 23.65)
Wakefulness After Sleep Onset (WASO) - mins	WMD = –7.06 min (95% CI –21.21 to 7.09) (Not statistically significant)	• Sedative-hypnotics: WMD –23.89 min (95% CI –44.46 to –3.32)
REM Latency [higher values worse]	WMD = +12.82 min (95% CI 8.11, 17.53)	• Eszopiclone: WMD +13.73 min (95% CI 8.85 to 18.61)
Sleep Latency	WMD = –4.44 min (95% CI –8.93 to 0.05) (Not statistically significant)	• Eszopiclone: WMD –4.29 min (95% CI –6.85 to –1.73)

New Guidelines:

High Quality Guidelines:

Department of Veterans Affairs and Department of Defense: Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea³

In 2025, the VA/DoD updated guidance for the management of chronic insomnia and OSA.³ Literature was reviewed through March 31, 2024 to support the revised recommendations.³ Drug therapy included daridorexant, doxepin, eszopiclone, lemborexant, suvorexant, zaleplon, zolpidem, ramelteon, antipsychotics, benzodiazepines, diphenhydramine, and trazodone.³ In adult patients with insomnia disorder, the guidelines evaluated 5 systematic reviews for the effectiveness of pharmacotherapy and included 2 systematic reviews and 2 RCTs for the effectiveness of behavioral treatment modalities on sleep outcomes.³ The behavioral treatment modalities included individual therapy, group therapy, guided self-help, digital CBT-I, telephone CBT-I, and unguided self-help.³ A sleep algorithm for the management of insomnia was developed that included the following best practices:³

- Use a patient-centered care approach and shared decision-making.

- Encourage non-pharmacologic approaches (e.g., CBT-I or BBT-I) before pharmacotherapy and consider sleep specialist referral in patients who do not respond to short-term pharmacotherapy.
- Before starting short-term pharmacotherapy, review patient sleep history, reproductive status, and evaluate contraindications for pharmacotherapy.
- Prior to starting pharmacotherapy, a deprescribing plan should be discussed and all patients offered a non-benzodiazepine benzodiazepine receptor agonist should be specifically counseled regarding the risk of complex sleep-related behaviors.

The Work Group used the GRADE approach for each recommendation and its strength using various domains including confidence in the recommendation quality, balance of desirable and undesirable outcomes, and patient values/preferences.³ Recommendations include:³

Behavioral and Psychological Treatments for Chronic Insomnia Disorder

- CBT-I treatment (FOR - Strong recommendation; moderate quality evidence)
 - The benefits of CBT-I, including reducing insomnia severity and improved sleep efficiency, significantly outweighed the potential harms.³
- BBT-I treatment (FOR - Weak recommendation; moderate quality evidence)
 - The benefits of BBT-I, including reducing insomnia severity and improved sleep efficiency, significantly outweighed the potential harms. However, there was a much smaller literature base for BBT-I, and the evidence on BBT-I evaluates its effect on older adults only.³
- Sleep hygiene education as a stand-alone treatment (AGAINST - Weak recommendation; low-quality evidence)³
 - Since CBT-I and BBT-I require trained professionals who may not always be readily available, or due to potential burdens of multiple appointments, it is suggested that providers seek out CBT-I resources or alternative strategies such as BBT-I or self-help or internet-based CBT-I programs.³
 - Providers should use a patient-centered, motivational interviewing approach to encourage reluctant patients to engage in CBT-I or BBT-I.³

Insomnia Pharmacotherapy if Offered by Provider

- CBT-I over pharmacotherapy as first-line treatment (FOR – Weak recommendation; low-quality evidence)³
 - There are overall less concerns for harm associated with CBT-I compared to hypnotic medications which may cause complex behaviors such as “sleep-driving” and worsening of depression, including suicidal thoughts and actions.³
- Use of either daridorexant, lemborexant, suvorexant, doxepin, eszopiclone, zaleplon, or zolpidem (FOR – Weak recommendation; low-quality evidence)
 - The benefits of pharmacotherapy for chronic insomnia (e.g., sleep efficiency, wake after sleep onset, and daytime functioning) slightly outweighed the potential harm of adverse events.³
- Use of antipsychotics, benzodiazepines, diphenhydramine, or trazodone (AGAINST – Weak recommendation; very low-quality evidence)
 - The benefits of antipsychotics, diphenhydramine, benzodiazepines, and trazodone were lacking. The potential harm of adverse events outweighed the benefits.³
- Use of ramelteon (NEITHER FOR NOR AGAINST No recommendation – very low-quality evidence)³
 - The benefits of ramelteon were inconsistent but slightly outweighed the potential harm, which was small.³

Oregon Health Authority: Mental Health Clinical Advisory Group⁴

In 2024, the MHCAG updated recommendations for management of chronic insomnia.⁴ The recommendations aim to improve patient sleep quality while minimizing medication-related harms. The clinical features of chronic insomnia disorder are outlined, and assessment tools are provided.⁴ An algorithm was developed to guide treatment for insomnia with CBT-I or medications.⁴ The guideline can be accessed here: <https://www.oregon.gov/oha/HPA/DSI->

[Pharmacy/MHCAGDocs/MHCAG_Treatment-of-Chronic-Insomnia-Disorder-in-Adults.pdf](#).⁴ Several links to evidence-based online resources are provided within the document.⁴

MHCAG Recommendations for Treatment of Chronic Insomnia Disorder in Adults⁴

- Use stepwise evidence-based approach to manage insomnia.⁴
 - Emphasize sleep hygiene, stimulus control, sleep restriction, limitations on stimulating or sedating foods, drinks or substances, proper timing of sleep-disturbing medications, and use relaxation techniques.⁴
 - Offer CBT-I to all patients as the initial treatment.⁴
 - CBT-I provides clinically meaningful long-term improvement in critical outcomes of remission, response, SOL, WASO and sleep quality (moderate-quality evidence).⁴
 - CBT-I treatment is usually 6 sessions, which can be provided in-person or via telemedicine. A minimum of 4 sessions is needed for treatment response.⁴
 - Several free online evidence-based CBT-I programs and mobile apps exist (payment-based programs and paid mobile apps are also available).⁴ See link above.
- Use shared decision-making when adding pharmacologic therapies.⁴
 - Discuss benefits, risks, costs, and patient preferences before prescribing medications.⁴
 - Reserve short-term pharmacotherapy for patients who cannot access CBT-I, who have persistent symptoms despite CBT-I, or who need temporary relief.⁴
- Use medications if necessary for limited duration (<4 weeks) such as:
 - Non-benzodiazepine hypnotics (zolpidem, eszopiclone) for sleep onset and/or sleep maintenance.⁴
 - Orexin receptor antagonists (lemborexant, suvorexant) or antidepressants (doxepin, trazodone) for sleep maintenance.⁴
 - Benzodiazepines (temazepam, triazolam) for severe insomnia with anxiety; use as needed for 7-10 days and plan for tapering; discouraged for long-term use.⁴
- Reassess medication efficacy and adverse effects within 2-4 weeks of initiation.
 - Avoid use of medications in patients with significant respiratory, hepatic, or renal impairment, or those with increased fall risk.⁴
 - Taper medications to minimize rebound insomnia and withdrawal.⁴
- Special Populations
 - Older adults: prioritize non-pharmacologic strategies; use lower doses and shorter durations if medications are needed.⁴
 - Comorbid psychiatric or medical conditions: tailor therapy to address both insomnia and the underlying disorder.⁴

Guidelines for Clinical Context

European Insomnia Guideline – Treatment Recommendations for Chronic Insomnia in Adults (2023 Update)³¹

In 2023, the European Insomnia Guideline was developed by a team of researchers and clinicians consisting of the European Sleep Research Society (ESRS), and the European Insomnia Network (EIN).³¹ Literature was reviewed from June 2016 through October 2022 (with another update added in May 2023) to support the revised recommendations.³¹ Behavioral therapies such as CBT-I and pharmacologic agents for the treatment of insomnia disorder were included in the updated clinical practice guideline.³¹ Drug therapy research included benzodiazepines, benzodiazepine receptor agonists, sedating antidepressants, antipsychotics, antihistamines, melatonin receptor agonists, and orexin receptor antagonists.³¹ In the update, the results of meta-analyses were used as the basis for grading

recommendations.³¹ Details regarding the quality of individual trials were not provided.³¹ Evidence was graded as “A = Very strong recommendation (high-quality evidence) or B = Strong recommendation (moderate-quality evidence).³¹ The treatment recommendations are summarized in **Table 6**.

Table 6. European Insomnia Guideline – Treatment Recommendations for Chronic Insomnia in Adults³¹

Treatment	Setting / Application	Recommended Duration	Evidence Grade
Cognitive Behavioral Therapy for Insomnia (CBT-I) – Face-to-face or guided digital (6-8 weekly sessions)	All adults (including comorbidities) as first line treatment	Typically, 4 to 8 weeks	A
Short-term pharmacotherapy (≤ 4 weeks): Benzodiazepines, BZRA, Daridorexant, low-dose sedating antidepressants	When CBT-I insufficient by itself	≤ 4 weeks	A (BZ/BZRA/Daridorexant) B (Antidepressants)
Longer-term pharmacotherapy (case-by-case): Orexin receptor antagonists, prolonged-release melatonin (≥ 55 years)	When benefits outweigh risks	Up to 3 months or more	A (Orexin antagonists) B (Melatonin)
Not recommended pharmacotherapies: Antihistamines, antipsychotics, fast-release melatonin, ramelteon, herbal remedies	All adults	n/a	A (against use)
Adjunctive non-pharmacological: Light therapy, Exercise	With CBT-I as augmentative support	20-30 minutes daily	B

Key: BZ = benzodiazepines; BZRA = benzodiazepine receptor agonists; CBT-I = Cognitive-Behavioral Therapy for Insomnia

After review, 6 guidelines were excluded due to poor quality.

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

Table 7. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Suvorexant ⁵¹	BELSOMRA	March 2025	Use in Special Populations	Suvorexant and its metabolite, hydroxy suvorexant, are present in low concentrations in breast milk. Developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for suvorexant and any potential adverse effects on the breastfed infant.
Daridorexant ⁵²	QUVIVIQ	Sept 2024	Warnings and Precautions	The effects of daridorexant on respiratory function should be considered if prescribed to patients with compromised respiratory function.
Lemborexant ⁵³	DAYVIGO	April 2023	Warnings and Precautions	The effects of lemborexant on respiratory function should be considered if prescribed to patients with compromised respiratory function.

Randomized Controlled Trials:

A total of 188 citations were manually reviewed from the initial literature search. After further review, most citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized below (**Table 8**). The full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials and Safety Studies.

Study	Comparison	Population	Primary Outcome	Results				Notes/Limitations
Yu Z, et al. ⁶¹	Doxepin (6 mg/day) vs. zolpidem (5-10 mg/day)	Adults with insomnia disorder	Sleep quality as measured by PSQI and PSG (WASO; TST; SOL; SE); Executive function as measured by the WSCT (64-card version); Safety measured by TESS	Outcome	Doxepin (n=53)	Zolpidem (n=56)	P-value	Excluded patients with other sleep disorders (e.g. OSA); inclusion and exclusion criteria not reported
				WASO (min)	80.3	132.9	<0.05	
				TST (min)	378.9	333.2	<0.05	
				SOL (min)	28.2	20.3	<0.05	
				SE (%)	77.8	68.6	<0.05	
				PSQI	6.1	7.9	<0.05	
				Adverse effects (%)	23	13	<0.05	
Cheng J, et al. ⁶²	Lemborexant 10 mg vs. placebo	Adult and older patients with and moderate-to-severe COPD	Difference in least-squares mean SpO ₂ during TST test from day 1 to day 8	Day 1 1. lemborexant: 91.1 (SD 2.8) 2. Placebo: 91.5 (SD 2.2) LSMD = -0.4 (95% CI -0.9 to 0.0); p=0.065 Not statistically significant Day 8 1. lemborexant: 91.3 (SD 2.2) 2. Placebo: 90.8 (SD 2.6) LSMD = 0.5 (95% CI 0.1 to 0.9); p=0.022				Not all patients had history of insomnia disorder (20% overall); Sample size was small; Low SpO ₂ levels (below 88–92%) may be associated with unfavorable clinical outcomes in patients with COPD. Although therapy did not demonstrate negative impact on SpO ₂ at day 8, safety beyond 8 days in this population unclear. Effect on COPD exacerbations or clinical symptoms of fatigue may be a more clinically relevant endpoint

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; min=minutes; LSMD = least squares mean difference; OSA=obstructive sleep apnea; PSG=polysomnography ; PSQI=Pittsburg Sleep Quality Index ; SD=standard deviation; SE=sleep efficiency ; SOL=sleep onset latency; SpO₂= peripheral oxygen concentration; TESS=treatment emergent symptom scale; TST=total sleep time ; WASO=wake after sleep onset ; WSCT=Wisconsin sorting card test

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
melatonin	MELATONIN	TABLET	Y
ramelteon	RAMELTEON	TABLET	Y
ramelteon	ROZEREM	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
daridorexant HCl	QUVIVIQ	TABLET	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP-AID	CAPSULE	N
diphenhydramine HCl	EZZ NITE SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP AID	LIQUID	N

diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	REST SIMPLY	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxylamine succinate	NIGHTTIME SLEEP AID	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
doxylamine succinate	SLEEP AID ULTRA	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
melatonin	MELATONIN	TAB RAPDIS	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
quazepam	DORAL	TABLET	N
quazepam	QUAZEPAM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	TASIMELTEON	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	ZOLPIDEM TARTRATE	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N

Appendix 2: Abstracts of Comparative Clinical Trials

Yu, Z., Han, L., Yan, P. et al. Doxepin is more effective than zolpidem in improving executive function in patients with insomnia disorder. *Sleep Breath* 28, 929–934 (2024).

Background

Insomnia disorder is associated with an impairment in cognitive performance. Doxepin and zolpidem have been found to be effective in improving sleep. In this study, we aimed to compare the effects of doxepin and zolpidem on sleep structure and executive function in patients with insomnia disorder.

Methods

Patients with primary insomnia were randomly assigned to receive doxepin 6 mg/day orally or zolpidem 5–10 mg/day orally. Polysomnography (PSG) and the Pittsburgh Sleep Quality Index (PSQI) were used at baseline and after the 8-week treatment to compare clinical efficacy in the two groups. Safety was assessed using the Treatment Emergent Symptom Scale (TESS). Executive function was evaluated using the Wisconsin sorting card test (WSCT).

Results

Of 120 patients enrolled in the study, 60 participants were assigned to each group. A total of 109 participants (53 in the doxepin group and 56 in the zolpidem group) completed the study. After treatment, the wake after sleep onset (WASO) and total sleep time (TST) values in the doxepin group were 80.3 ± 21.4 min and 378.9 ± 21.9 min, respectively, which were significantly better than those in the zolpidem group (132.9 ± 26.5 min and 333.2 ± 24.2 min, respectively; $P < 0.05$). The sleep onset latency (SOL) value in the zolpidem group (20.3 ± 4.7 min) was significantly better than that in the doxepin group (28.2 ± 5.6 min; $P < 0.05$). The sleep efficiency (SE) in the doxepin group was $77.8 \pm 4.2\%$, which was significantly better than that in the zolpidem group ($68.6 \pm 5.0\%$; $P < 0.05$). The PSQI score of the doxepin group was 6.1 ± 1.1 , which was significantly lower than that in the zolpidem group (7.9 ± 1.9 ; $P < 0.05$). The treatment adverse events in the doxepin group was 23.3%, which was significantly higher than that in the zolpidem group (13.3%; $P < 0.05$). The WSCT showed a significant improvement in persistent errors (PE), random errors (RE), and categories in the two groups after 8-week treatment, and the improvement in RE and the categories was more obvious in the doxepin group ($P < 0.05$).

Conclusions

Both doxepin and zolpidem were found to be effective in improving sleep quality, but the effects exhibited different patterns. Doxepin improved executive function more effectively than zolpidem in patients with insomnia disorder.

Cheng JY, Lorch D, Hall N, Moline M. Respiratory safety of lemborexant in adult and elderly subjects with moderate-to-severe chronic obstructive pulmonary disease. *J Sleep Res.* 2025;34(2):e14334.

Background: Because some hypnotics worsen respiratory conditions, it was important to determine the respiratory safety of lemborexant, a competitive dual orexin-receptor antagonist approved to treat adults with insomnia, in subjects with moderate-to-severe chronic obstructive pulmonary disease.

E2006-A001-113 (Study 113; NCT04647383) was a multicentre, multiple-dose, randomised, double-blind, placebo-controlled, two-period crossover study in adult subjects with moderate or severe chronic obstructive pulmonary disease (per spirometry-based Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria).

Methods: Subjects ($N = 30$) were randomised to two treatment sequences comprising 8-night treatment periods (washout ≥ 14 days) with lemborexant 10 mg or placebo. Peripheral oxygen saturation (SpO₂; primary endpoint), apnea-hypopnea index, objective sleep parameters and sleep architecture measures were assessed after single (Day 1) and multiple (Day 8) doses.

Results: There was no significant difference in least-squares mean SpO₂ after a single dose of lemborexant (91.1%) versus placebo (91.5%). Although a statistically significant difference in SpO₂ was observed after multiple doses (least-squares mean: lemborexant, 91.3%; placebo, 90.8%) favouring lemborexant, this was not considered clinically meaningful. Apnea-hypopnea index was not significantly different between treatments after single or multiple doses. Total sleep time and total rapid eye movement sleep were significantly greater on Days 1 and 8 with lemborexant versus placebo. Treatment-emergent adverse events were reported in five (16.7%) subjects when taking lemborexant and four (13.3%) subjects when taking placebo; treatment-emergent adverse events were mostly mild.

Conclusion: Lemborexant was well tolerated and did not adversely impact SpO₂ or apnea-hypopnea index after single and multiple doses relative to placebo in subjects with moderate-to-severe chronic obstructive pulmonary disease.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 21, 2025

1	exp Melatonin/	25487
2	exp Zolpidem/	1847
3	exp Eszopiclone/	150
4	zaleplon.mp.	474
5	ramelteon.mp.	601
6	exp Diphenhydramine/	4606
7	exp Doxylamine/	414
8	exp Doxepin/	871
9	exp Flurazepam/	783
10	exp Temazepam/	682
11	exp Triazolam/	1251
12	exp Estazolam/	124
13	lemborexant.mp.	225
14	suvorexant.mp.	514
15	daridorexant.mp.	144
16	exp Midazolam/	10367
17	exp Sleep Aids, Pharmaceutical/	9476
18	exp Orexin Receptor Antagonists/	701
19	exp Benzodiazepines/	72318
20	tasimelteon.mp.	108
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	107884
22	exp "Sleep Initiation and Maintenance Disorders"/	20787
23	exp Sleep Wake Disorders/	122671
24	22 or 23	122671
25	21 and 24	5541
26	limit 25 to yr="2022 -Current"	632
27	limit 26 to (english language and humans)	562
28	limit 27 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	188

Appendix 4: Key Inclusion Criteria

Population	Patients with insomnia
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1 or placebo
Outcomes	Outcomes Sleep latency (SL) Total sleep time (TST) Wake after sleep onset (WASO) Quality of sleep (QOS) Sleep efficiency (SE) Number of awakenings (NOA)
Timing	4 weeks or longer
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Sedatives

Goals:

- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent inappropriate long-term use of sedatives.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- 1 month to 12 months (criteria-specific)

Requires PA:

- Non-preferred products
- Preferred sedatives when:
 - There is history of a recent opioid OR
 - Long-term use beyond 4 weeks every 120 days (except melatonin in children and adolescents).
- Melatonin is not covered for adults over 18 years of age.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org

- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #3
3. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment (CBT-I), failed to have benefit in symptoms after at least 4 5-6 CBT interventions, OR have inability to access CBT-I? Note: CBT-I may be offered through telehealth or with provider <u>or patient</u> -directed, internet-based apps.	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness.
4. Is the request for long-term therapy beyond 30 days?	Yes: Go to #5	No: Go to #6
5. Is this request for continuation of therapy previously approved by the fee-for-service pharmacy program?	Yes: Go to Renewal Criteria.	No: Go to #6
6. Is there documentation that the prescriber plans to reassess the patient for medication efficacy and adverse effects within 2-4 weeks of initiation OR for patients already started on treatment, documentation of reassessment 2-4 weeks after initiation? Note: Sedative medications should be prescribed only if necessary and for limited duration. (<4 weeks)	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
7. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	Yes: Inform prescriber of preferred alternatives in class. Go to #8	No: Go to #8
8. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	Yes: Approve for 5 years	No: Go to #9
9. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	Yes: Go to #10	No: Go to #12
10. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	Yes: Go to #12 Document reason for switch.	No: Go to #11
11. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	Yes: Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	No: Pass to RPh. Deny; medical appropriateness.
12. Is the request for treatment of chronic insomnia disorder?	Yes: Go to #13	No: Go to #14

Approval Criteria		
13. Is there documentation or provider attestation that the patient does not have any contraindications to therapy? Contraindications could include: ○ Narcolepsy ○ Untreated obstructive sleep apnea (OSA) ○ Suicidal ideation or high suicide risk ○ Severe hepatic impairment (e.g. Child-Pugh C) ○ Active substance use disorder	Yes: Approve for 30 days.	No: Pass to RPh. Deny; medical appropriateness.
14. RPh only: Is the request for an FDA-approved indication or is there medical evidence of benefit for the prescribed sedative?	Yes: Document supporting literature and approve for 30 days with subsequent approvals dependent on follow-up and documented response.	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #15
15. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	Yes: Go to #16 Document baseline severity	No: Pass to RPh. Deny; medical necessity.
16. Is the request for a melatonin agonist (e.g., melatonin, ramelteon, tasimelteon) for treatment of one of the following circadian rhythm sleep-wake disorders: • People with delayed sleep-wake phase disorder • Adults with non-24 hour sleep-wake disorder • Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder?	Yes: Approve for approve 30 days with subsequent approvals dependent on follow-up and documented response.	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a slow taper plan?	Yes: Approve for duration of taper (not to exceed 3 months). Subsequent requests should document progress toward discontinuation	No: Go to #2
2. Is the request to treat insomnia disorder and has the patient already received 1 month of treatment with a sedative hypnotic?	Yes: Go to #3	No: Go to #4
3. Has the patient been evaluated by a sleep specialist?	Yes: Go to #4	No: If not eligible for EPSDT review: Pass to RPh. Deny; medical appropriateness. If eligible for EPSDT review: Go to #5
4. Is there documentation based on medical records that the patient and provider have discussed whether benefits of ongoing therapy (hospitalizations, function, quality of life) continue to outweigh risks (memory problems, dementia, cognitive impairment, daytime sedation, falls, fractures, dependence, and reduced long-term efficacy)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of improvement (e.g., of symptoms, function, quality of life, etc) since treatment was started?	Yes: Approve for 3 months	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 02/26(DE);12/22; 8/22; 12/20; 7/18; 3/17; 11/14, 3/14, 5/06, 2/06, 11/05, 9/05, 2/04, 2/02, 9/01
Implementation: [TBD](#); 1/1/24; 10/1/22; 1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05

Drug Class Update: Medications for Allergies **(Nasal Allergy Inhalers, 1st Generation Antihistamines, 2nd Generation Antihistamines)**

Date of Review: February 2026

Date of Last Review: August 2022

Dates of Literature Search: 05/25/2022 – 10/24/2025

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Review new evidence for intranasal allergy inhalers and oral antihistamines for use in chronic rhinosinusitis, allergic rhinitis, and urticaria. The prescription medications have Food and Drug Administration (FDA) approval for management of seasonal and/or perennial allergic rhinitis, which is not currently funded by the Oregon Health Plan (OHP), unless the patient has a co-morbidity such as asthma.

Plain Language Summary:

- Rhinitis refers to inflammation of the nasal passages. This inflammation can cause many symptoms including sneezing, itching, nasal congestion, and runny nose. Allergic rhinitis is caused by a reaction to pollen from trees, grasses, and weeds, dust mites, molds, and animal dander that are breathed in from the environment.
- Treatment of allergic rhinitis includes reducing exposure to allergen and other triggers combined with medicines. Nasal sprays that contain antihistamines or steroids are frequently recommended to relieve symptoms. Some medicines are available without a prescription (over the counter) while others require a prescription.
- Chronic spontaneous urticaria is itching that has lasted for more than 6 weeks with no known cause. Antihistamines such as cetirizine, loratadine, or fexofenadine may relieve the constant itching.
- The Oregon Health Authority (OHA) will pay for fluticasone nasal spray for people who are less than 21 years of age and will pay for the oral antihistamines cetirizine and loratadine without needing documentation as to why it is needed. For all other medicines, providers must explain to the OHA why someone needs the medicine before OHA will pay for it. This process is called prior authorization

Research Questions:

1. Do nasal corticosteroids, antihistamines, or mast cell stabilizers differ in safety or effectiveness when used to treat allergic rhinitis?
2. Do oral antihistamines differ in safety or effectiveness when used to treat allergic rhinitis or urticaria?

3. Are there subgroups of patients based on demographics (e.g., age, race, gender), concomitant comorbidities and medications, or pregnancy status, for which one nasal inhaler or oral antihistamine is more effective or associated with fewer harms?

Conclusions:

- No recently published, high-quality systematic reviews were identified.
- A 2023 international guideline updated recommendations for evaluation and treatment of allergic rhinitis.¹ Intranasal corticosteroids are strongly recommended as first-line therapy for management of allergic rhinitis.¹ Second-generation oral antihistamines are strongly recommended for management of allergic rhinitis.¹ Intranasal antihistamines are recommended as first- or second-line therapy.¹ Cromolyn is recommended as second-line therapy.¹
- Canada's Drug Agency (CDA) recommends that RYALTRIS, the combination olopatadine/mometasone nasal spray should not be reimbursed by Canadian public drug plans for the symptomatic treatment of moderate-to-severe seasonal allergic rhinitis and associated ocular symptoms in adults, adolescents, and children aged 6 years and older.² Evidence from 3 clinical trials (2 in adolescent and adult patients with seasonal allergic rhinitis and 1 in children with seasonal allergic rhinitis) demonstrated that olopatadine/mometasone nasal spray improved nasal and eye symptoms in people with seasonal allergic rhinitis compared to placebo.² However, compared to monotherapy with mometasone nasal spray, the improvements were not clinically meaningful in adolescents and adults, and there was no comparative evidence available in children.²
- The 2021 publication from the British Association of Dermatologists provides evidence-based recommendations for the management of chronic spontaneous urticaria.³ Most of the evidence is derived from studies in adult patients as there is very little published evidence for pediatric patients aged less than 12 years.³ Recommendations focused on antihistamines include:
 - First-line antihistamines for managing chronic spontaneous urticaria in children include chlorpheniramine, cetirizine, desloratadine, loratadine, and fexofenadine (Expert Opinion).³
 - For people with chronic spontaneous urticaria offer a second-generation H₁-antihistamine (cetirizine, desloratadine, fexofenadine, loratadine, levocetirizine) using a regular daily licensed dose (Strong Recommendation).³
 - Do not offer first-generation H₁ antihistamines routinely, unless there is no alternative due to concerns about their short- and long-term effects on the central nervous system (Strong Recommendation).³
 - Do not increase the dose of first generation H₁ antihistamines (Strong Recommendation).³
- In 2024, XHANCE (fluticasone) nasal spray received expanded FDA approval for treatment of adults with chronic rhinosinusitis (CRS) without nasal polyps.⁴³ Prior to this approval, fluticasone nasal spray was approved for treatment of CRS with nasal polyps.⁴³
- There is insufficient evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one treatment for those with allergic rhinitis is more effective or associated with fewer adverse events.

Recommendations:

- After a review of recent evidence, no changes to the Preferred Drug List (PDL) are recommended.
- Create a PDL class for the first-generation oral antihistamines.
- Remove prior authorization (PA) for preferred nasal inhalers in adults.
- Review drug costs in executive session.

Summary of Prior Reviews and Current Policy:

- The intranasal allergy drugs were reviewed by the Pharmacy and Therapeutics (P & T) Committee at the August 2022 meeting. No changes were made to the PDL based on review of recently published evidence. Prior authorization criteria were removed for intranasal allergy products in children and adolescents 20 years of age and younger with rhinitis to enhance the ability to grow, develop, or participate in school per the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Medicaid benefit.
- The second-generation oral antihistamines were last reviewed by the P & T Committee in May 2015. A Drug Effectiveness Review Project (DERP) systematic review summarized the available evidence that was shared with the Committee. Comparative systematic reviews and trials found insufficient evidence to support superior efficacy/effectiveness or harms of any single second-generation antihistamine. The first-generation oral antihistamines have never been reviewed by the P & T Committee.
- All non-preferred intranasal allergy medications and oral antihistamines require PA for Oregon Health Plan (OHP) funded indications. Fluticasone propionate is the only preferred drug on the PDL, and all other intranasal corticosteroids are non-preferred (**Appendix 1**). Non-steroid intranasal allergy drugs are non-preferred due to lack of evidence for OHP-funded conditions. Cetirizine and loratadine are the preferred second-generation oral antihistamines, all other antihistamines are nonpreferred and require PA (**Appendix 1**). Use of non-preferred intranasal corticosteroids and oral antihistamines for OHP-funded conditions is restricted as outlined in the PA criteria in **Appendix 3**.

Background:

Allergic Rhinitis

Allergic rhinitis is an immunoglobulin (Ig) E-mediated condition that occurs after exposure to indoor or outdoor allergens, such as dust mites, insects, animal dander, molds, and pollen.⁴ Symptoms include rhinorrhea, sneezing, nasal congestion, and itching of the nose, eyes, ears, and throat.⁵ Allergic rhinitis affects up to 60 million people in the United States annually, can have a major impact on quality of life, and poses a substantial economic burden on society.⁶ Self-reported rates of allergic rhinitis are 10% to 30% of adults and as many as 40% of children in the United States.⁶ A report from the American Academy of Allergy, Asthma & Immunology (AAAAI) estimates that about 19 million employed adults have allergic rhinitis, and that approximately \$4.5 billion in direct costs and 3.8 million in lost work and school days are attributable to this disease annually.⁷ Allergic rhinitis is also a significant cause of decreased work productivity/presenteeism (work interference) and school performance.⁶ Allergic rhinitis can, by itself, introduce significant inattention, impaired cognition, and decreased daytime school performance.⁶ Quality of life issues associated with rhinitis include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits.⁶

Validated clinical surveys for allergic rhinitis often include questions about congestion, rhinorrhea and/or sneezing and may either be representative of current symptoms or reflective of a period of days or weeks.⁸ One patient reported outcome measure is the Total Nasal Symptom (TNS-4) score, which is typically administered as a survey comprised of 4 questions about runny nose, nasal itching, sneezing, and congestion.⁸ The TNS-4 score is the sum of scores for each of the 4 symptoms, measured on an ordinal scale of 0, 1, 2 or 3 representing no symptoms, mild, moderate, or severe symptoms respectively for a maximum score of 12.⁹ The TNS-4 is the most accepted primary efficacy variable that is rated for drug approval in allergic rhinitis by the Food and Drug Administration (FDA).¹⁰ Relatively few articles have calculated minimal clinically important difference (MCID) scores for allergic rhinitis outcome measures, and those that have suggest widely different approaches.¹¹ The Agency for Healthcare Research and Quality (AHRQ) recommended the MCID be equal to 30% of the maximum TNS-4 score (i.e., ± 3.6 points on a 12 point scale).¹¹ The 12-hour reflective total nasal symptoms score (rTNSS) has also been reported in clinical studies evaluating efficacy of intranasal products.¹¹ Both morning and evening assessments are added together so the rTNSS can range from 0 to 24 points.¹¹ For the rTNSS scale of 0 to 24 points, the comparable MCID thresholds would be 0.46 points (by regression analysis) or 0.56 points (by meta-analysis).¹¹ Despite the very small change in

scoring, which calls into question significant clinical benefit, there are no other validated methods to determine MCID for clinical trials of allergic rhinitis medications.¹¹

Symptoms of rhinitis are classified based on the temporal pattern (seasonal, perennial, or episodic), frequency, and severity.⁴ Mild rhinitis severity is present when symptoms are not interfering with quality of life such as impairment of daily activities, work or school performance, leisure activities, and sleep.⁶ Moderate or severe rhinitis is present when symptoms are troublesome or there is negative impact on any of these quality of life parameters.⁶ Symptom frequency has been divided into intermittent (less than 4 days per week or less than 4 consecutive weeks per year) and persistent (4 or more days per week and 4 or more consecutive weeks per year).⁶ Allergic rhinitis may also be classified by the temporal pattern of environmental exposure to a triggering allergen: 1) seasonal (e.g., from pollens); 2) perennial (year-round, e.g., dust mites); or 3) from episodic allergen exposures not normally encountered in the patient’s environment, such as visiting a home with pets.⁶ In the United States, allergic rhinitis has traditionally been viewed as either seasonal or perennial, and it is this classification system that the FDA uses when approving new medications for allergic rhinitis.⁶

Second-generation oral antihistamines (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine) are recommended for management of allergic rhinitis.⁶ The overall efficacy of first-generation antihistamines (e.g., diphenhydramine, hydroxyzine, chlorpheniramine) compared with second-generation antihistamines for the management of allergic rhinitis symptoms has not been adequately studied.⁶ The older first-generation antihistamines are lipophilic and readily cross the blood-brain barrier.¹² This causes unwanted adverse effects such as sedation, drowsiness, fatigue, and impaired concentration, and memory as well as anti-muscarinic effects.¹² The second-generation antihistamines are highly selective for the histamine H₁ receptor, lipophobic, and have limited penetration across the blood-brain barrier which minimizes their adverse effects.¹² Because of significant side effects, first-generation antihistamines have not been recommended for the treatment of allergic rhinitis.¹²

Intranasal pharmacologic options for the treatment of rhinitis include corticosteroids, antihistamines, mast cell stabilizers, and anticholinergics (see **Table 1**). Intranasal corticosteroids are the mainstay of treatment for persistent allergic rhinitis.⁵ Specific intranasal corticosteroid agents include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone.¹³ Mometasone, fluticasone furoate, ciclesonide, and triamcinolone are approved by the Food and Drug Administration (FDA) for use in children 2 years of age and older.¹³ They act by decreasing the influx of inflammatory cells and inhibiting the release of cytokines, thereby reducing inflammation of the nasal mucosa.⁵ Intranasal corticosteroids also help reduce symptoms of sneezing, itching, rhinorrhea, and congestion.⁶ Limited data suggest that intranasal corticosteroids can also reduce allergic eye symptoms, such as itching, tearing, redness, and puffiness.⁶ In comparative studies, intranasal corticosteroids have shown superior efficacy to oral antihistamines and leukotriene inhibitors in controlling nasal symptoms, with no significant difference in the relief of ocular symptoms.¹⁴ There is no evidence that one intranasal corticosteroid is superior over another product.⁵ Onset of action for intranasal corticosteroids starts at time points ranging from 3 to 5 hours to 60 hours after first dosing.¹⁴ Patients with known seasonal allergic rhinitis should start prophylactic treatment with intranasal corticosteroids several days before the pollen season with an evaluation of the patient's response in 2 weeks.¹⁴

Table 1. Nasal Allergy Medications: Indications and Age Ranges.^{15,16}

Drug Name (Trade Name)	FDA Indication(s)	Formulation	OTC
Intranasal Antihistamines			
Azelastine (ASTEPRO ALLERGY, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	205.5 mcg/spray	YES
Azelastine (ASTEPRO)	Seasonal Allergic Rhinitis; ≥ 2 yo to 6 yo Perennial Allergic Rhinitis; ≥ 6 months to 6 yo	137 mcg/spray	NO

Olopatadine (PATANSASE, generic)	Seasonal Allergic Rhinitis ≥6 yo	665 mcg/spray	NO
Combination Intranasal Antihistamine/Corticosteroids			
Azelastine-Fluticasone propionate (DYMISTA, generic)	Seasonal Allergic Rhinitis ≥6 yo	137 mcg-50 mcg/spray	NO
Olopatadine-Mometasone (RYALTRIS)	Seasonal Allergic Rhinitis ≥12 yo	665 mcg-25mcg/spray	NO
Intranasal Corticosteroids			
Beclomethasone dipropionate (BECONASE AQ)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis; Nonallergic Rhinitis; Nasal Polyps ≥6 yo	42 mcg/spray	NO
Beclomethasone (QNASL)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥4 yo	40 mcg and 80 mcg/spray	NO
Budesonide (RHINOCORT ALLERGY, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	32 mcg/spray	YES
Ciclesonide (OMNARIS)	Seasonal Allergic Rhinitis ≥6 yo Perennial Allergic Rhinitis ≥12 yo	50 mcg/spray	NO
Ciclesonide (ZETONNA)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥12 yo	37 mcg/spray	NO
Flunisolide (generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis ≥6 yo	25 mcg/spray	NO
Fluticasone furoate (FLONASE SENSIMIST)	Allergic Rhinitis ≥2 yo	27.5 mcg/spray	YES
Fluticasone propionate (FLONSASE ALLERGY RELIEF, generic)	Seasonal Allergic Rhinitis; Perennial Allergic Rhinitis; Nonallergic Rhinitis ≥4 yo	50 mcg/spray	YES
Fluticasone propionate (EXHANCE)	Nasal polyps ≥ 18 yo	93 mcg/spray	NO
Mometasone (NASONEX, generic)	Seasonal Allergic Rhinitis ≥2 yo	50 mcg/spray	YES
Triamcinolone (NASACORT ALLERGY 24 HOUR, generic)	Allergic Rhinitis ≥2 yo	50 mcg/spray	YES
Intranasal Mast Cell Stabilizer			
Cromolyn (generic)	Allergic Rhinitis ≥2 yo	5200 mcg/spray	YES
Intranasal Anticholinergics			
Ipratropium (generic)	Rhinorrhea associated with Perennial Allergic Rhinitis; Seasonal Allergic Rhinitis; and Nonallergic Rhinitis ≥5 yo	21 mcg and 42 mcg/spray	NO
Abbreviations: FDA = Food and Drug Administration; mcg = micrograms; mg = milligrams; OTC = over the counter; yo = years old			

The most common local adverse effects of intranasal corticosteroids include nasal dryness, throat irritation, burning, hoarseness, sneezing, and bitter aftertaste.¹⁷ The effect of intranasal corticosteroids on growth in children has been investigated in controlled studies using both knemometry in short-term studies (2 to 4 weeks) and stadiometry in long-term (12 months) studies.¹⁴ A meta-analysis of 8 randomized controlled trials (n=755) with appropriate controls showed that, compared to children using placebo, mean growth was significantly lower among children using intranasal corticosteroids in trials using knemometry (n = 4 studies) and that there was no significant growth difference in studies using stadiometry (n = 4 studies).¹⁸ The data suggests that intranasal corticosteroids might have deleterious effects on short-term growth in children, but the heterogeneity in the stadiometry studies makes the effects on long-term growth suppression unclear.¹⁴ All intranasal corticosteroids carry a warning that long-term use may restrict growth in children, so using the lowest effective dose is advised to avoid negative growth effects.¹⁹

Two intranasal antihistamines, azelastine and olopatadine, are FDA-approved for the treatment of allergic rhinitis. Intranasal antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than intranasal corticosteroids, and show consistent

reduction in symptoms and improvement in quality of life in randomized controlled trials (RCTs) compared to placebo.¹⁴ They are less effective for nasal congestion than intranasal corticosteroids.¹⁴ For relief of symptoms of seasonal allergic rhinitis, intranasal antihistamines are equal or superior to oral antihistamines, and may benefit patients for whom oral antihistamine treatment fails.⁶ Intranasal antihistamines have a more rapid onset of 15 to 30 minutes compared to 150 minutes for oral antihistamines and have fewer adverse effects than oral therapy.⁶ Adverse effects observed with intranasal antihistamines include a bitter aftertaste, headache, nasal irritation, epistaxis, and sedation.⁴ Although intranasal antihistamines are an option if symptoms do not improve with nonsedating oral antihistamines, their use as first- or second-line therapy is limited by adverse effects and twice daily dosing.²⁰ Either intranasal antihistamines or intranasal corticosteroids may be offered as first-line monotherapy for nonallergic rhinitis.⁶

Intranasal cromolyn is available over the counter and is thought to inhibit the degranulation of mast cells, thereby preventing histamine release.⁴ Although safe for general use, it is not considered first-line therapy for allergic rhinitis because it is less effective than intranasal corticosteroids and is administered three or four times daily.²¹ Although evidence supports the use of intranasal ipratropium, an anticholinergic, for severe rhinorrhea, it is not effective for other nasal symptoms.²² Adverse effects of ipratropium include dryness of the nasal mucosa, epistaxis, and headache.⁴ The recommended administration is two to three times daily.⁴

Oral decongestants are medications that act on adrenergic receptors, which leads to vasoconstriction of small blood vessels (such as those in the nasal mucosa), resulting in relief of nasal congestion symptoms in allergic rhinitis.¹ The most commonly used oral decongestants are pseudoephedrine and phenylephrine, which are sympathomimetic vasoconstrictors that differ in their selectivity to adrenoceptors.¹ Due to the oral administration of pseudoephedrine and phenylephrine, both drugs act systemically and can lead to side effects such as insomnia, headache, nervousness, anxiety, tremors, palpitations, urinary retention, increased blood pressure, and other adverse effects.¹

Intranasal decongestants (oxymetazoline, xylometazoline, and phenylephrine) are alpha-adrenergic agonists acting as topical vasoconstrictors reducing edema/tissue thickness. Clinically, short-term use results in reduction of nasal congestion/blockage, with little to no effect on allergic symptoms such as sneezing, rhinorrhea, or nasal itching.¹ Onset of action is within 10 minutes, and duration of the effect lasts up to 12 hours.¹ Intranasal decongestants can be helpful for short-term relief of nasal congestion. Intranasal decongestants can provide effective short-term relief of nasal congestion in patients with allergic rhinitis during an acute flare, but chronic use is not recommended due to risk of rhinitis medicamentosa (increased symptomatic nasal congestion secondary to medication overuse).¹

Leukotriene receptor antagonists (LTRAs) have been studied in the treatment of allergic rhinitis.¹ Montelukast is approved by the FDA for the treatment of seasonal allergic rhinitis in adults and children over 2 years of age, and for perennial allergic rhinitis in adults and children over 6 months of age.¹ While LTRA monotherapy has been consistently shown to be superior to placebo for the treatment of allergic rhinitis, there is now significant evidence that alternative inhaled nasal corticosteroids are superior to LTRAs in terms of symptom reduction and quality of life improvement.¹ In March 2020, the FDA announced a safety concern regarding montelukast and potential serious neuropsychiatric events, including suicidal thoughts.¹ A boxed warning, the FDA's most prominent warning, was added to prescribing information.¹ The FDA advised further that in allergic rhinitis, montelukast should be reserved for patients who are not treated effectively with or cannot tolerate other allergy medications.¹

Allergic rhinitis is also often associated with asthma, allergic conjunctivitis, atopic dermatitis, rhinosinusitis, and sleep apnea.⁶ Allergic rhinitis, is notably present in about 75% to 80% of all patients with asthma and in nearly 100% with allergic asthma, is associated with increased asthma-related hospitalizations and higher total annual medical costs.⁶ Intranasal use of antihistamines and mast cell stabilizers has not been adequately studied in conditions outside of allergic rhinitis.

However, intranasal corticosteroids have been studied and used for several other conditions that are currently funded by the Oregon Health Plan (OHP). For example, allergic rhinitis and asthma are often comorbid diseases. An epidemiologic association between allergic rhinitis and asthma has been consistently demonstrated across patient populations. Given the association, it is hypothesized that reducing inflammation in the upper airway with an intranasal corticosteroid may improve asthma symptoms.²³ Attempts have also been made to reduce frequency of episodes of obstructive sleep apnea by changing the characteristics of the upper airway using therapies such as intranasal corticosteroids.²⁴ Acute sinusitis is frequently caused by a viral infection and is a common reason for primary care visits. Inflammation of nasal mucosa plays an essential role in the development of sinusitis. In addition to treating seasonal and perennial rhinitis, corticosteroids might be beneficial in reducing inflammation in the treatment of sinusitis.²⁵ Lastly, chronic rhinosinusitis (CRS) is a group of disorders characterized by chronic inflammation of the mucosa of the nose and paranasal sinuses, with symptoms that persist for more than 12 weeks without complete resolution of symptoms.²⁶ It is most commonly classified as CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The use of corticosteroids for the management of CRS is supported by a high level of evidence, with particularly strong evidence for CRSwNP.²⁶

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (also known as chronic idiopathic urticaria) is defined as recurrent pruritic hives with or without angioedema for more than 6 weeks.²⁷ Chronic urticaria affects about 1% of the world population of all ages, mostly young and middle-aged women.²⁸ It generally lasts for several years (longer than 1 year in 25–75% of patients) and often takes more than one year before effective management is implemented.²⁸ Lesions result from degranulation of cutaneous mast cells, which leads to the release of histamine, the major mediator of pruritic wheals and angioedema, as well as the release of leukotrienes, prostaglandins, and platelet-activating factors.²⁹ Proinflammatory cytokines and vasoactive factors are also released, which results in vasodilatation and leakage of plasma from the vascular system in and below the skin.²⁹ Although most cases of chronic urticaria are idiopathic, this condition has been reported in association with infections (e.g., hepatitis B and C, Epstein–Barr virus, herpes simplex virus, mycoplasma, Helicobacter pylori, helminthic infestation), rheumatologic diseases (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis), thyroid disease, neoplasms (particularly lymphoreticular cancers and other lymphoproliferative disorders), ovarian tumors, and oral contraceptive use.²⁹

A joint initiative of Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) resulted in publication of 2018 guidance for diagnosis and management of chronic urticaria.³⁰ The use of patient-reported outcome measures such as the urticaria activity score (UAS), the angioedema activity score (AAS), the CU quality of life questionnaire (CU-Q2oL), the angioedema quality of life questionnaire (AE-QoL) and the urticaria control test (UCT) in studies and clinical practice has helped to better define the effects and impact of CU on patients.³⁰ The UAS7 is based on the assessment of key urticaria signs and symptoms (wheals and pruritus), which are documented by the patient over 7 consecutive days using a 4 point scale. A score of 0 indicates no itching or wheals, while a score of 3 indicates intense wheals (> 50 wheals/24 hours) and intense itching as presented in **Table 2**.³⁰ The UCT has only 4 items with a clearly defined cut-off for patients with “well-controlled” versus “poorly controlled” disease, and it is thus suited for the management of patients in routine clinical practice.³⁰ The cut-off value for a well-controlled disease is 12 of 16 possible points.³⁰

Table 2. The Urticaria Activity Score for Assessing Disease Activity in Chronic Spontaneous Urticaria³⁰

Score	Wheals	Pruritus
0	None	None
1	Mild (< 20/24 hours)	Mild (present but not annoying or troublesome)
2	Moderate (20-50/24 hours)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (> 50/24 hours)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

First-line CSU treatment recommendations include oral second-generation antihistamines (cetirizine, loratadine, fexofenadine) taken on a regular basis at standard doses instead of as needed (PRN) for itching.²⁹ Second-generation antihistamines have advantages over first-generation antihistamines (e.g., chlorpheniramine, cyproheptadine, hydroxyzine, diphenhydramine) because of a slower histamine receptor dissociation rate, thus a longer duration of action; less central nervous system penetration making them less soporific, and minimal activity at nonhistaminic receptors, thus reducing their likelihood for significant side effects.³¹ Adults with CSU unresponsive to standard second-generation antihistamine dosing may require dosing increased up to four times the recommended daily dose to manage symptoms (also known as up-dosing).²⁹ There is less evidence and formal guidance for up-dosing second-generation antihistamines in children.²⁹

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews: No recent, high-quality systematic reviews were identified.

After review, 11 systematic reviews were excluded due to poor quality (e.g., indirect network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).³²⁻⁴²

New Guidelines:

High Quality Guidelines:

International Consensus Statement on Allergy And Rhinology: Allergic Rhinitis

A 2023 international guideline updated recommendations for evaluation and treatment of allergic rhinitis.¹ In this publication, the second and third generation antihistamines are classified as newer-generation antihistamines and include cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.¹ First-generation antihistamines (e.g., diphenhydramine and chlorpheniramine) have anticholinergic side effects and can cross the blood–brain barrier, resulting in central nervous system effects such as sedation and drowsiness.¹ These side effects can be more pronounced in the elderly, so first-generation antihistamines should be used with caution in this population.¹ Newer-generation antihistamines block peripheral histamine₁-receptors without crossing the blood–brain barrier which prevents central nervous system side effects.¹ Several newer-generation antihistamines are metabolized in the liver by cytochrome P450 enzymes.¹ As a result, prescribers should be conscious of concomitant administration of other drugs that are either processed by cytochrome P450 or drugs that are cytochrome P450 inducers because concurrent administration can either increase or decrease the plasma concentration of the antihistamine.

The data existing on the use of H₂ antihistamines in allergic rhinitis is limited in scope and quality, with very little addition to the literature in the past decade.¹ The objective findings of improved nasal airway resistance suggest that the H₂ histamine receptor does modulate nasal tissue response to histamine.¹ However, the clinical significance of this mechanism is not clear, particularly in the context of modern treatment algorithms.¹ Given the relatively manageable side effect profile and costs of H₂ antihistamines, they may offer patients with otherwise recalcitrant allergic rhinitis symptoms an additional treatment option. However, additional investigation on the efficacy of H₂ antihistamines in combination with other topical medications may be beneficial in the future.¹

Intranasal antihistamines (azelastine, olopatadine) were compared to oral antihistamine monotherapy in 8 studies, with superiority of intranasal antihistamine in 3 studies, and equivalency in 5 studies.¹ Most of the included studies set a minimum enrollment age of 12 years or older. Three studies that included children aged between 6 and 12 years old found superiority of intranasal antihistamine to placebo in improving symptoms and quality of life.¹ No study reported any serious adverse effects from use of an intranasal antihistamine.¹ These formulations are noted to be generally well tolerated, with taste aversion being the most reported adverse effect.¹ Olopatadine was reported to have better sensory attributes than azelastine in one study.¹ Other reported adverse effects were uncommon, with somnolence, headache, epistaxis, and nasal discomfort each occurring in less than 10% of patients treated with azelastine or olopatadine.¹

Intranasal corticosteroids are first-line therapy for the treatment of allergic rhinitis by virtue of their superior efficacy in controlling nasal symptoms.¹ The benefits of using intranasal corticosteroids outweigh the risks when used to treat seasonal or perennial allergic rhinitis.¹ Intranasal corticosteroid sprays have undesirable local adverse effects, such as epistaxis, with increased frequency compared to placebo in prolonged administration studies.¹ There are no apparent negative effects on the hypothalamic-pituitary axis.¹

The results in head-to-head comparisons between antihistamine and pseudoephedrine monotherapy are contradictory.¹ While some studies showed that antihistamine monotherapy was more effective than pseudoephedrine, other studies have had different findings.¹ Monotherapy with either treatment (i.e., pseudoephedrine or antihistamine) was more effective than placebo.¹ An analysis of the effectiveness of phenylephrine compared to placebo has shown that phenylephrine (up to 40 mg six times daily) is not superior to placebo in relieving nasal congestion symptoms in allergic rhinitis.¹ Little evidence for benefit in controlling symptoms other than nasal congestion.¹ In certain cases, combination therapy with an oral antihistamine may be beneficial to alleviate severe nasal congestion in short courses.¹ Although not recommended for routine use in allergic rhinitis, pseudoephedrine can be effective in reducing nasal congestion; however, it should only be used as short-term/rescue therapy after a discussion of the risks and benefits with the patient (comorbidities) and consideration of alternative intranasal therapy options.¹

Cromolyn is a mast cell stabilizer that inhibits the release of mast cell mediators that promote IgE-mediated inflammation.¹ It has a rapid onset of action with efficacy lasting up to 8 hours, taken as one spray 3-6 times daily.¹ Ultimately, the role of cromolyn as a primary treatment for allergic rhinitis is limited given its lower efficacy when compared to intranasal corticosteroids and potential compliance challenges secondary to a frequent dosing regimen.¹ The medication can also be administered as a preventive strategy, prior to allergen exposure to reduce the development of allergic rhinitis symptoms.¹ A summary of pharmacotherapy recommendations and strength of evidence are presented in **Table 3**.

Table 3. Pharmacotherapy Recommendations for Treatment of Allergic Rhinitis¹

Medication	Grade of Evidence	Policy	Interpretation
Second Generation Antihistamines	A	Strong Recommendation For Use in Allergic Rhinitis	Newer-generation oral antihistamines are strongly recommended.
Cromolyn	A	Recommend For a Second-Line Treatment Use in Allergic Rhinitis	Primarily used to prevent the onset of symptoms prior to allergen exposure, but it also can be used to treat symptoms once they occur. Less effective for nasal symptoms compared to intranasal antihistamines and intranasal corticosteroids.
Intranasal Antihistamines	A	Recommendation For Use in Allergic Rhinitis	Intranasal antihistamines should be used as first- or second-line therapy.
Intranasal Corticosteroids	A	Strong Recommendation For Use in Allergic Rhinitis	Intranasal corticosteroids should be used as first-line therapy
Intranasal Decongestants	B	Option For Use in Allergic Rhinitis	Option for short-term use
Leukotriene Receptor Antagonists	A	Recommend Against	Leukotriene receptor antagonists should not be used as monotherapy.
Oral Corticosteroids	B	Strong Recommendation Against Use in Allergic Rhinitis	Oral corticosteroids are not recommended.
Oral Decongestants	A	Strong Recommendation Against Use in Allergic Rhinitis	Not recommended for routine treatment. Short-term use of combination H1 antihistamine and oral decongestant may be considered.
First Generation Antihistamines	B	No Recommendation	Insufficient data

Canada's Drug Agency: Recommendations for Coverage of Olopatadine/Mometasone Nasal Spray

Canada's Drug Agency (CDA) recommends that RYALTRIS, the combination olopatadine/mometasone nasal spray should not be reimbursed by Canadian public drug plans for the symptomatic treatment of moderate-to-severe seasonal allergic rhinitis and associated ocular symptoms in adults, adolescents, and children aged 6 years and older.² Evidence from 3 clinical trials (2 in adolescent and adult patients with seasonal allergic rhinitis and 1 in children with seasonal allergic rhinitis) demonstrated that olopatadine/mometasone nasal spray improved nasal and ocular symptoms in people with seasonal allergic rhinitis compared to placebo.² However, compared to monotherapy with mometasone nasal spray, the improvements were not clinically meaningful in adolescents and adults, and there was no comparative evidence available in children.² Based on the evidence reviewed during the initial meeting and the reconsideration meeting, the Canadian Drug Expert Committee (CDEC) could not determine whether olopatadine/mometasone nasal spray would address the unmet needs of patients because of the uncertainty around the benefit of this combination therapy versus appropriate active comparators.²

British Association of Dermatologists: Guidance for Management of Chronic Urticaria

The 2021 publication from the British Association of Dermatologists provides evidence-based recommendations for the management of urticaria.³ Most of the evidence is derived from studies in adult patients as there is very little published evidence for pediatric patients aged less than 12 years.³ Recommendations focused on antihistamines include:

- Consider using appropriate validated scoring systems to assess disease activity and impact, for example Dermatology Life Quality Index (DLQI), weekly Urticaria Activity Score 7 (UAS7), Angioedema Activity Score (AAS) and/or Urticaria Control Test (UCT) (Expert Opinion).³
- First-line antihistamines for managing chronic urticaria in children include chlorpheniramine, cetirizine, desloratadine, loratadine, and fexofenadine (Expert Opinion).³
- For people with chronic spontaneous urticaria offer a second-generation antihistamine (cetirizine, desloratadine, fexofenadine, loratadine, levocetirizine) using a regular daily licensed dose (Strong Recommendation).³
- Do not offer first-generation H₁ antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system (Strong Recommendation).³
- Do not up dose (i.e. increasing the dose above the licensed dose) first generation antihistamines (Strong Recommendation).³
- Offer up dosing (i.e. increasing the dose above the licensed dose) of a single second-generation antihistamine, by up to fourfold the licensed dose, to people whose symptoms are inadequately controlled by the standard licensed dose, provided it is tolerated and there is no caution or contraindication (Strong Recommendation).³
- Consider montelukast, in addition to a second-generation H₁-antihistamine, in people whose symptoms are inadequately controlled by standard and increased doses of second-generation H₁-antihistamines (Weak Recommendation).

New Formulations or Indications:

March 2024: XHANCE (fluticasone) nasal spray received expanded FDA-approval for treatment of adults with chronic rhinosinusitis (CRS) without nasal polyps.⁴³ The recommended dose is 186 mcg (1 spray per nostril) or 372 mcg (2 sprays per nostril) twice daily.⁴³ Prior to this approval, fluticasone nasal spray was approved for treatment of CRS with nasal polyps.⁴³ Efficacy of fluticasone nasal spray in patients with CRS without nasal polyps was evaluated in two 24-week, placebo-controlled RCTs.⁴³ In both trials, patients were randomized 1:1:1 to receive fluticasone 186 mcg twice daily, fluticasone 372 mcg twice daily, or placebo, all administered nasally for 24 weeks.⁴³ All patients enrolled had at least 2 active nasal symptoms (congestion/obstruction, discharge, facial pain or pressure, reduction or loss of smell) with a minimum nasal congestion score of at least 1.5 out of 3 and a baseline CT scan showing at least 25% opacification of both ethmoid and at least 1 maxillary sinus.⁴³

In both trials, the coprimary efficacy endpoints were 1) change from baseline at Week 4 in the composite symptom score (CSS) as determined by patients using a daily diary and 2) change from baseline at Week 24 in percent opacified sinus volume.⁴³ CSS was the sum of the individual nasal symptom scores for congestion/obstruction, facial pain/pressure, and nasal discharge, each rated by the patient on a 0 to 3 categorical severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) in the morning immediately prior to the next dose.⁴³ Total CSS ranges from 0 to 9.⁴³ Sinus opacification was measured by CT scan and scored using a 3-dimensional computer-assisted volumetric assessment using software to quantify the average percent of opacified volume in the ethmoid and maxillary sinuses.⁴³ In Trial 3 fluticasone was statistically more efficacious than placebo in relieving symptoms and reducing sinus volume. In Trial 4 fluticasone only showed more efficacy in reducing symptoms compared to placebo, but no difference in opacified sinus volume. Results from both trials are presented in **Table 4**. The most common adverse events reported with fluticasone nasal spray in patients with CRS without nasal polyps were epistaxis, headache, and nasopharyngitis.⁴³

Table 4. Least Square Mean Change in Composite Symptom Scores at Week 4 and Percent Opacified Sinus Volume at Week 24⁴³

	Placebo	Fluticasone 186 mcg BID	Fluticasone 372 mcg BID	Difference (95% CI) 186 mcg BID vs. Placebo	Difference (95% CI) 372 mcg BID vs. Placebo
Trial 3	N=75	N=72	N=73		
Baseline Mean CSS	6.2	5.9	6.0	-0.7 (-1.3 to -0.2)	-0.9 (-1.5 to -0.4)
LSM change from baseline in CSS at Week 4	-0.8	-1.5	-1.7		
Baseline Percent of Opacified Sinus Volume	64.1	60.5	61.5	-7.5 (-12.1 to -2.8)	-5.9 (-10.6 to -1.3)
LSM change from baseline in Percent Opacified Sinus Volume at Week 24	0.4	-7.0	-5.5		
Trial 4	N=41	N=41	N=40		
Baseline Mean CSS	5.7	5.5	5.8	-0.9 (-1.6 to -0.2)	-0.9 (-1.6 to -0.2)
LSM change from baseline in CSS at Week 4	-0.7	-1.6	-1.6		
Baseline Percent of Opacified Sinus Volume	61.9	63.0	60.7	-0.5 (-6.8 to 5.9)	-3.2 (-9.5 to 3.2)
LSM change from baseline in Percent Opacified Sinus Volume at Week 24	-5.3	-5.7	-8.4		
Abbreviations: BID = twice daily; CI = confidence interval; CSS = composite symptom score; LSM = least square mean; N=number					

Randomized Controlled Trials:

A total of 136 citations were manually reviewed from the initial literature search. After further review, 136 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Nasal Inhalers

Generic	Brand	Route	Form	PDL	OTC
fluticasone propionate	FLUTICASONE PROPIONATE	NASAL	SPRAY SUSP	Y	F
fluticasone propionate	XHANCE	NASAL	AER BR.ACT	N	F
beclomethasone dipropionate	QNASL	NASAL	HFA AER AD	N	F
beclomethasone dipropionate	QNASL CHILDREN	NASAL	HFA AER AD	N	F
ciclesonide	ZETONNA	NASAL	HFA AER AD	N	F
triamcinolone acetonide	24 HOUR NASAL ALLERGY	NASAL	SPRAY	N	O
flunisolide	FLUNISOLIDE	NASAL	SPRAY	N	F
ipratropium bromide	IPRATROPIUM BROMIDE	NASAL	SPRAY	N	F
triamcinolone acetonide	NASAL ALLERGY	NASAL	SPRAY	N	O
flunisolide	NASALIDE	NASAL	SPRAY	N	F
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	NASAL	SPRAY	N	O
fluticasone propionate	24 HOUR ALLERGY	NASAL	SPRAY SUSP	N	O
fluticasone propionate	ALLERGY RELIEF	NASAL	SPRAY SUSP	N	O
fluticasone propionate	FLUTICASONE PROPIONATE	NASAL	SPRAY SUSP	N	O
mometasone furoate	ALLERGY NASAL	NASAL	SPRAY/PUMP	N	O
azelastine HCl	AZELASTINE HCL	NASAL	SPRAY/PUMP	N	F
azelastine/fluticasone	AZELASTINE-FLUTICASONE	NASAL	SPRAY/PUMP	N	F
budesonide	BUDESONIDE	NASAL	SPRAY/PUMP	N	O
azelastine/fluticasone	DYMISTA	NASAL	SPRAY/PUMP	N	F
mometasone furoate	MOMETASONE FUROATE	NASAL	SPRAY/PUMP	N	F
mometasone furoate	MOMETASONE FUROATE	NASAL	SPRAY/PUMP	N	O
mometasone furoate	NASONEX 24HR ALLERGY	NASAL	SPRAY/PUMP	N	O
olopatadine HCl	OLOPATADINE HCL	NASAL	SPRAY/PUMP	N	F
ciclesonide	OMNARIS	NASAL	SPRAY/PUMP	N	F
olopatadine HCl/mometasone	RYALTRIS	NASAL	SPRAY/PUMP	N	F
budesonide	BUDESONIDE	NASAL	SPRAY/PUMP		O

First Generation Oral Antihistamines

Generic	Brand	Route	Form	PDL	OTC
carbinoxamine maleate	CARBINOXAMINE	ORAL	LIQUID		F
carbinoxamine maleate	CARBINOXAMINE MALEATE	ORAL	LIQUID		F
carbinoxamine maleate	CARBINOXAMINE PD	ORAL	LIQUID		F
carbinoxamine maleate	CARBZAH	ORAL	LIQUID		F
			SUS ER		
carbinoxamine maleate	CARBINOXAMINE MALEATE ER	ORAL	12H		F
			SUS ER		
carbinoxamine maleate	KARBINAL ER	ORAL	12H		F

carbinoxamine maleate	CARBINOXAMINE MALEATE	ORAL	TABLET	F
carbinoxamine maleate	RYVENT	ORAL	TABLET	F
chlorpheniramine maleate	ED CHLORPED JR	ORAL	SYRUP	O
			TAB	
chlorpheniramine maleate	CHLO-AMINE	ORAL	CHEW	O
chlorpheniramine maleate	ALLER-CHLOR	ORAL	TABLET	O
chlorpheniramine maleate	ALLERGY	ORAL	TABLET	O
chlorpheniramine maleate	ALLERGY RELIEF	ORAL	TABLET	O
chlorpheniramine maleate	ALLERGY-TIME	ORAL	TABLET	O
clemastine fumarate	CLEMASTINE FUMARATE	ORAL	SYRUP	F
clemastine fumarate	CLEMASTINE FUMARATE	ORAL	TABLET	F
clemastine fumarate	CLEMSZA	ORAL	TABLET	F
cyproheptadine HCl	CYPROHEPTADINE HCL	ORAL	SYRUP	F
cyproheptadine HCl	CYPROHEPTADINE HCL	ORAL	TABLET	F
dexbrompheniramine maleate	ALA-HIST IR	ORAL	TABLET	O
dexchlorpheniramine maleate	RYCLORA	ORAL	SOLUTION	F
	DEXCHLORPHENIRAMINE		TABLET	
dexchlorpheniramine maleate	MALEATE	ORAL	ER	F
diphenhydramine HCl	ALLERGY	ORAL	CAPSULE	O
diphenhydramine HCl	ALLERGY RELIEF	ORAL	CAPSULE	O
diphenhydramine HCl	BANOPHEN	ORAL	CAPSULE	O
diphenhydramine HCl	DIPHENHYDRAMINE HCL	ORAL	CAPSULE	F
diphenhydramine HCl	DIPHENHYDRAMINE HCL	ORAL	CAPSULE	O
diphenhydramine HCl	DIPHENHYDRAMINE HCL	ORAL	ELIXIR	F
diphenhydramine HCl	ALLERGY RELIEF	ORAL	LIQUID	O
diphenhydramine HCl	CHILDREN'S ALLERGY	ORAL	LIQUID	O
diphenhydramine HCl	CHILDREN'S ALLERGY RELIEF	ORAL	LIQUID	O
diphenhydramine HCl	DIPHEDRYL	ORAL	LIQUID	O
diphenhydramine HCl	DIPHENHYDRAMINE HCL	ORAL	LIQUID	O
diphenhydramine HCl	M-DRYL	ORAL	LIQUID	O
diphenhydramine HCl	SILADRYL DAS	ORAL	LIQUID	O
diphenhydramine HCl	ANTITUSSIVE COUGH SYRUP	ORAL	SYRUP	O
diphenhydramine HCl	HYDRAMINE	ORAL	SYRUP	O
			TAB	
diphenhydramine HCl	CHILDREN'S ALLERGY RELIEF	ORAL	CHEW	O
diphenhydramine HCl	ALLER-G-TIME	ORAL	TABLET	O
diphenhydramine HCl	ALLERGY	ORAL	TABLET	O
diphenhydramine HCl	ALLERGY RELIEF	ORAL	TABLET	O
diphenhydramine HCl	BANOPHEN	ORAL	TABLET	O
diphenhydramine HCl	DIPHENHYDRAMINE HCL	ORAL	TABLET	O

hydroxyzine HCl	HYDROXYZINE HCL	ORAL	SOLUTION		F
hydroxyzine HCl	HYDROXYZINE HCL	ORAL	TABLET		F
hydroxyzine pamoate	HYDROXYZINE PAMOATE	ORAL	CAPSULE		F
hydroxyzine pamoate	VISTARIL	ORAL	CAPSULE		F
pyrilamine maleate	PEDIACLEAR-8	ORAL	LIQUID		O
triprolidine HCl	HISTEX PD	ORAL	DROPS		O
triprolidine HCl	HISTEX PD	ORAL	DROPS	N	O
triprolidine HCl	HISTEX PDX	ORAL	DROPS	N	O
triprolidine HCl	PEDIACLEAR PD	ORAL	DROPS		O
triprolidine HCl	TRIPROLIDINE HCL	ORAL	DROPS		O
triprolidine HCl	HISTEX	ORAL	LIQUID		O
			TAB		
triprolidine HCl	HISTEX	ORAL	CHEW	N	O

Second-Generation Antihistamine

Generic	Brand	Route	Form	PDL	OTC
loratadine	ALLERGY RELIEF	ORAL	SOLUTION	Y	O
cetirizine HCl	CETIRIZINE HCL	ORAL	SOLUTION	Y	O
loratadine	CHILDREN'S ALLERGY	ORAL	SOLUTION	Y	O
loratadine	CHILDREN'S ALLERGY RELIEF	ORAL	SOLUTION	Y	O
loratadine	CHILDREN'S LORATADINE	ORAL	SOLUTION	Y	O
loratadine	LORATADINE	ORAL	SOLUTION	Y	O
loratadine	LORATADINE ALLERGY	ORAL	SOLUTION	Y	O
			TAB		
loratadine	ALLERGY RELIEF	ORAL	RAPDIS	Y	O
			TAB		
loratadine	LORATADINE	ORAL	RAPDIS	Y	O
cetirizine HCl	ALL DAY ALLERGY	ORAL	TABLET	Y	O
loratadine	ALL DAY ALLERGY RELIEF	ORAL	TABLET	Y	O
loratadine	ALLERCLEAR	ORAL	TABLET	Y	O
cetirizine HCl	ALLERGY RELIEF	ORAL	TABLET	Y	O
loratadine	ALLERGY RELIEF	ORAL	TABLET	Y	O
cetirizine HCl	CETIRIZINE HCL	ORAL	TABLET	Y	O
loratadine	LORATADINE	ORAL	TABLET	Y	F
loratadine	LORATADINE	ORAL	TABLET	Y	O
cetirizine HCl	ALL DAY ALLERGY RELIEF	ORAL	CAPSULE	N	O
loratadine	ALLERGY RELIEF	ORAL	CAPSULE	N	O
			ORAL		
fexofenadine HCl	CHILDREN'S ALLERGY	ORAL	SUSP	N	O
cetirizine HCl	CETIRIZINE HCL	ORAL	SOLUTION	N	F

cetirizine HCl	CETIRIZINE HCL	ORAL	SOLUTION	N	O
cetirizine HCl	CHILDREN'S ALL DAY ALLERGY	ORAL	SOLUTION	N	O
cetirizine HCl	CHILDREN'S ALLERGY RELIEF	ORAL	SOLUTION	N	O
cetirizine HCl	CHILDREN'S CETIRIZINE HCL	ORAL	SOLUTION	N	O
levocetirizine	LEVOCETIRIZINE				
dihydrochloride	DIHYDROCHLORIDE	ORAL	SOLUTION	N	F
cetirizine HCl	CETIRIZINE HCL	ORAL	TAB CHEW	N	O
loratadine	CHILDREN'S ALLERGY RELIEF	ORAL	TAB CHEW	N	O
cetirizine HCl	CHILDREN'S CETIRIZINE HCL	ORAL	TAB CHEW	N	O
loratadine	CHILDREN'S LORATADINE	ORAL	TAB CHEW TAB	N	O
desloratadine	DES Loratadine	ORAL	RAPDIS	N	F
levocetirizine					
dihydrochloride	24HR ALLERGY RELIEF	ORAL	TABLET	N	O
fexofenadine HCl	ALLER-EASE	ORAL	TABLET	N	O
fexofenadine HCl	ALLERGY RELIEF	ORAL	TABLET	N	O
levocetirizine					
dihydrochloride	ALLERGY RELIEF	ORAL	TABLET	N	O
desloratadine	CLARINEX	ORAL	TABLET	N	F
desloratadine	DES Loratadine	ORAL	TABLET	N	F
fexofenadine HCl	FEXOFENADINE HCL	ORAL	TABLET	N	F
fexofenadine HCl	FEXOFENADINE HCL	ORAL	TABLET	N	O
levocetirizine	LEVOCETIRIZINE				
dihydrochloride	DIHYDROCHLORIDE	ORAL	TABLET	N	F
levocetirizine	LEVOCETIRIZINE				
dihydrochloride	DIHYDROCHLORIDE	ORAL	TABLET	N	O

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to October 17, 2025> - Steroid Nasal Inhalers

1	exp Beclomethasone/	3147
2	exp Budesonide/	5356
3	ciclesonide.mp.	506
4	flunisolide.mp.	391
5	exp Fluticasone/	3540
6	exp Mometasone Furoate/	962
7	exp Triamcinolone Acetonide/ or exp Triamcinolone/	10371
8	Nasal Absorption/ or Administration, Intranasal/	17788
9	1 or 2 or 3 or 4 or 5 or 6 or 7	22608
10	8 and 9	1027
11	exp Asthma/	150082
12	exp Sleep Apnea Syndromes/	47720
13	exp Sinusitis/	25085
14	exp Rhinitis, Allergic/	25124
15	11 or 12 or 13 or 14	237939
16	10 and 15	730
17	limit 16 to (english language and humans and yr="2022 -Current")	32

Ovid MEDLINE(R) ALL <1946 to October 17, 2025> - Antihistamine Nasal Inhalers

1	azelastine.mp.	851
2	exp Olopatadine Hydrochloride/	318
3	exp Ipratropium/	1934
4	exp Cromolyn Sodium/	4144
5	exp Nasal Absorption/ or exp Administration, Intranasal/	17788
6	1 or 2 or 3 or 4	7104
7	5 and 6	358
8	exp Sleep Apnea Syndromes/	47720
9	exp Sinusitis/	25085
10	exp Asthma/	150082
11	exp Rhinitis, Allergic/	25124
12	8 or 9 or 10 or 11	237939
13	7 and 12	241
14	limit 13 to (english language and humans and yr="2022 -Current")	16

Ovid MEDLINE(R) ALL <1946 to October 24, 2025> - Oral Antihistamines

1	Histamine H1 Antagonists/ or Histamine Antagonists/ or carbinoxamine.mp.	21868
2	Chlorpheniramine/	2016
3	Clemastine/	357
4	Cyproheptadine/	2276
5	dexchlorpheniramine.mp.	185
6	Diphenhydramine/	4122
7	Hydroxyzine/	1472
8	Pyrilamine/	1797
9	tripolidine.mp.	7
10	Loratadine/	1306
11	Cetirizine/	1490
12	fexofenadine.mp.	1186
13	levocetirizine.mp.	577
14	desloratadine.mp.	780
15	exp Rhinitis, Allergic/th [Therapy]	4864
16	exp Urticaria/th [Therapy]	1683
17	15 or 16	6532
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	33068
19	17 and 18 5	51
20	limit 19 to (english language and humans and yr="2015 -Current")	88

Intranasal Allergy Drugs

Goals:

- Restrict use of intranasal allergy inhalers for conditions funded by the OHP and where there is evidence of benefit.
- Treatment for allergic or non-allergic rhinitis is funded by the OHP only if it complicates asthma, sinusitis or obstructive sleep apnea. Only intranasal corticosteroids have evidence of benefit for these conditions.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- 30 days to 12 months

Requires PA:

- ~~Preferred intranasal corticosteroids without prior claims evidence of asthma for people 21 years of age and older.~~
- ~~Preferred intranasal antihistamines for people 21 years of age and older.~~
- Non-preferred intranasal corticosteroids and antihistamines
- Intranasal ipratropium and cromolyn sodium

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/
- Preferred intranasal corticosteroids, preferred antihistamines DO NOT require prior authorization for children and adolescents up to their 21st birthday.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. ~~Is the prescribed drug intranasal ipratropium or cromolyn?~~	~~Yes: Pass to RPh. Deny; not funded by the OHP~~	~~No: Go to #3~~

Approval Criteria

~~3.~~ <u>2.</u> Does patient have <u>an evidence-supported and</u> co-morbid conditions funded by the OHP? - Chronic Sinusitis (-J320-J329) - Acute Sinusitis (J0100; J0110; J0120; J0130; J0140; J0190) - Sleep Apnea (G4730; G4731; G4733; G4739)	Yes: Document ICD10 code(s) and approve for up to 12 months for chronic sinusitis or sleep apnea and approve for no more than 30 days for acute sinusitis	No: Go to #<u>34</u>
~~4.3.~~ Is there a diagnosis of asthma or reactive airway disease in the past 1 year (J4520-J4522; J45901-J45998)?	Yes: Go to #<u>45</u>	No: Go to #<u>56</u>
~~5.4.~~ Is there a claim for an <i>orally</i> inhaled corticosteroid in the past 90 days? <u>Note:</u> Asthma-related outcomes are not improved by the addition of an intranasal corticosteroid to an orally inhaled corticosteroid.	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for up to 6 months
~~6.5.~~ Is the prescribed drug a preferred product?	Yes: Go to #<u>87</u>	No: Go to #<u>67</u>
~~7.6.~~ <u>Has the patient had lack of benefit, intolerance, or have a contraindication</u> ~~Will the prescriber consider switching to a preferred products?~~ <u>Note:</u> Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	Yes: Inform prescriber of preferred alternatives. Go to #<u>78</u>	No: Go to #<u>78</u>
~~8.7.~~ Is the patient eligible for EPSDT review AND is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	Yes: Approve for 6 months	No: Go to #<u>89</u>

Approval Criteria

9-8. RPh only: Is the diagnosis funded by the OHP?

Funded: Deny; medical appropriateness.

(e.g, COPD; Obstructive Chronic Bronchitis; or other Chronic Bronchitis [J449; J40; J410-418; J42; J440-449])

Use clinical judgment to APPROVE for 1 month to allow time for appeal.

Message: "The request has been denied because it is considered medically inappropriate; however, it has been APPROVED for 1 month to allow time for appeal."

Not Funded: Deny; not funded by the OHP.

(e.g, allergic rhinitis (J300-J309); chronic rhinitis (J310-312); allergic conjunctivitis (H1045); upper respiratory infection (J069); acute nasopharyngitis (common cold) (J00); urticaria (L500-L509); etc.)

P&T / DUR Review: 2/26 (DM); 8/22 (DM); 11/15 (AG); 7/15; 9/08; 2/06; 9/04; 5/04; 5/02
Implementation: TBD; 10/1/22; 10/13/16; 1/1/16; 8/25/15; 8/09; 9/06; 3/06; 5/05; 10/04; 8/02

Oral Antihistamines

Goals:

- Approve antihistamines only for conditions funded by the OHP in adults. Allow case-by-case review for members covered under the EPSDT program.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with Oregon Asthma Guidelines and medical evidence.

<http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx>

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred oral antihistamines and combinations

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	Yes: Inform prescriber of covered alternatives in class.	No: Go to #3
3. Does patient have a diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharyngitis?	Yes: Go to #4	No: Go to #8
4. Does the patient have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis or allergies?	Yes: Go to #5	No: Go to #6

Approval Criteria		
5. Does the drug profile show an asthma controller medication (e.g. ORAL corticosteroid, etc.) and/or inhaled rescue beta-agonist (e.g. albuterol, ICS/formoterol) within the last 6 months? <i>Keep in mind: albuterol may not need to be used as often if asthma is controlled on other medications.</i>	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness. <i>Oregon Asthma guidelines recommend all asthma clients have access to rescue inhalers and those with persistent disease should use anti-inflammatory medicines daily (preferably orally inhaled corticosteroids).</i>
6. Does patient have other co-morbid conditions or complications that are funded? • Acute or chronic inflammation of the orbit • Chronic Sinusitis • Acute Sinusitis • Sleep apnea • Wegener's Granulomatosis	Yes: Document ICD-10 codes. Go to #7	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #10
7. Does patient have contraindications (e.g. pregnancy), or had insufficient response to available treatment alternatives for the funded condition? Document.	Yes: Approve for up to 6 months	No: Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis COPD or Obstructive Chronic Bronchitis?	Yes: Pass to RPh. Deny; medical appropriateness. Antihistamine not indicated.	No: Go to #9

Approval Criteria		
9. Is the diagnosis funded? Note: Chronic Bronchitis, acute upper respiratory infections, and urticarial are not funded by the OHP	Yes: Pass to RPh. Deny; medical appropriateness	No: If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #10
10. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	Yes: Go to #11	No: Pass to RPh. Deny; medical necessity.
11. Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	Yes: Approve for 12 months.	No: Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class.

P&T Review: 2/26 (DM); 12/22; 5/15 (AG); 9/10; 9/08; 2/06; 9/04; 5/04; 2/02
Implementation: TBD; 1/1/23; 5/1/16; 7/15, 1/11, 7/09, 7/06, 3/06, 10/04, 8/02, 9/06

Drug Class Review: Ophthalmic Medication for Allergies

Date of Review:

End Date of Literature Search: 10/31/2025

Purpose for Class Review:

Review the evidence for the safety and efficacy of ophthalmic eye preparations used to manage allergic conjunctivitis as a pathway to coverage will be necessary once the Health Evidence Review Committee (HERC) benefit plan update is implemented in January 2027. Currently allergic conjunctivitis is not funded by HERC and over-the-counter versions of ophthalmic allergy medications are currently not covered.

Plain Language Summary:

- Conjunctivitis is an inflammation of the conjunctiva. The conjunctiva is the thin membrane that lines the inner surface of the eyelids and the whites of the eyes. Conjunctivitis can affect children and adults.
- There are many potential causes of conjunctivitis, including bacterial or viral infections and allergies. The most common symptoms of conjunctivitis include red eyes, itching, burning and discharge.
- Treatment of allergic conjunctivitis includes avoiding allergy triggers and lubricating eye drops which are available without a prescription. For symptoms that are bothersome, antihistamine eye drops can relieve itching and redness.
- The Drug Utilization Management and Research team recommends making some eye drops used to treat allergic conjunctivitis available without prior authorization for people with Oregon Health Plan insurance.

Research Questions:

1. What is the comparative efficacy for ophthalmic preparations used to treat allergic conjunctivitis?
2. Do ophthalmic preparations differ in safety when used to treat allergic conjunctivitis?
3. Are there specific subpopulations for which one ophthalmic drop or ointment is better tolerated or more effective than other available ophthalmic preparations when used to manage allergic conjunctivitis?

Conclusions:

- There is limited high-quality comparative evidence to evaluate safety and efficacy of ophthalmic preparations indicated for management of allergic conjunctivitis.
- Two systematic reviews published in 2015 identified moderate-quality evidence that showed azelastine and olopatadine ophthalmic drops are effective in reducing ocular itch when compared to placebo.^{1,2}
 - There were limited data to inform if some treatments are more effective than others.¹
 - Results from one meta-analysis suggested that olopatadine may be more effective than ketotifen in relieving itching, although there was high statistical heterogeneity between the 4 studies included in the analysis.¹
 - Moderate-quality evidence showed olopatadine has similar efficacy to ketotifen and epinastine in relieving ocular itch.²

- Alcaftadine appears to have a superior effect in reducing ocular itch compared to topical olopatadine (moderate-quality evidence).²
- Poor quality of reporting challenged the synthesis of evidence, and there was large variability in reporting outcomes.¹ The overall quality of the studies and reporting was poor, and most studies had small sample sizes.¹ Trials only evaluated short-term effects, with a range of treatment of one to eight weeks.¹
- No high-quality clinical practice guidelines have been published to guide treatment of allergic conjunctivitis.
- There is insufficient evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one treatment for those with allergic conjunctivitis is more effective or associated with fewer adverse events.

Recommendations:

- Create a new PDL class, “Ophthalmic Medications for Allergies”.
- Make at least one prescription product preferred without prior authorization. Defer to costs as clinical evidence does not differentiate products.
- Evaluate costs in executive session to identify which ophthalmic products should be preferred and if over the counter products should be covered.

Background:

Ocular allergies are a heterogeneous collection of immunoglobulin (Ig)E- and non-IgE-mediated conditions.³ Ocular allergy includes seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and contact blepharoconjunctivitis (CBC).³ The pathophysiology of allergic conjunctivitis is mediated by IgE-related mast cell activation, with release of histamine and other mediators promoting further immune cell activation and inflammation.⁴ Seasonal allergic conjunctivitis and PAC account for most ocular allergies (95%-98%) and AKC and VKC represent an estimated 2% of all ocular allergies.³ Classification and clinical features of ocular allergic conditions are presented in **Table 1**. Allergic conjunctivitis or conjunctival symptoms are present in 30-71% of patients with allergic rhinitis.⁵ Seasonal allergic conjunctivitis and PAC can affect between 14% to 45% of the general population, depending on geographical region.⁶ Ocular allergy is often underdiagnosed because only 10% of patients with ocular allergy symptoms seek medical attention, as most patients manage with over-the-counter medications and nonpharmacological remedies.⁷

Table 1. Classification and Clinical Features of Ocular Allergic Conditions³

Feature	Seasonal Allergic Conjunctivitis	Perennial Allergic Conjunctivitis	Vernal Keratoconjunctivitis	Atopic Keratoconjunctivitis	Contact Blepharoconjunctivitis
Pattern and Frequency	Intermittent, usually spring	Persistent	Persistent, worse in spring and summer	Persistent with exacerbations	Intermittent or persistent
Comorbid Conditions	Allergic rhinitis, allergic asthma	Allergic rhinitis, allergic asthma	Allergic rhinitis	Atopic dermatitis, allergic rhinitis, asthma	Contact dermatitis of other skin sites, remote from the eyes
Age and Sex	Childhood and young adult onset	Childhood and young adult onset	Childhood: ends by age 20 years. Male prevalence greater than female.	Usually, adults aged 30 to 50 years, can start in childhood. Male prevalence greater than female.	Middle-aged or older. Female prevalence greater than male.

Trigger	Pollen	Dust mite, animal dander, other perennial allergens	Grass pollen, tree pollen, hot and humid environment	Spring and summer seasonal or perennial allergens may worsen	Cosmetics, metals, or medications near the eye
Pathophysiology	IgE	IgE	IgE or non-IgE	IgE	Non-IgE
Abbreviations: IgE = Immunoglobulin E					

Four symptoms characterize ocular allergies: redness, itchiness, swelling, and watering (tearing).³ Many ocular allergy symptoms overlap with those of dry eye, with more than 50% of patients with ocular allergy also having dry eyes.³ A detailed history is essential to prevent misdiagnosis of serious conditions that have potential consequences such as vision loss.³ In particular, VKC and AKC require an ophthalmological evaluation for diagnosis and a close follow-up.⁵ Evaluation should not only focus on eliciting symptoms but should also include laterality, duration, triggers, previous treatments, contact lens use, family history, comorbid asthma, comorbid allergic rhinitis, exposures (occupational, environmental, and topical such as cosmetics), and history of ocular surgery, as these are important considerations in making a diagnosis.³

The 4 symptom domains of redness, itchiness, swelling, and watering (tearing) constitute an unvalidated questionnaire called the Total Ocular Symptom Score (TOSS) which can be used for describing symptom severity and monitoring treatment response.³ Scoring is based upon frequency of symptoms as: 4) all of the time; 3) most of the time; 2) half of the time; 1) some of the time; and 0) none of the time.³ The only Quality of Life (QoL) questionnaire available for ocular allergy pertains specifically to VKC. The QoL in VKC children (QUICK) questionnaire grades frequency of ocular allergy on a 3-point scale (1 = never, 2 = sometimes, and 3 = always) to assess disease status.³

The recommended management approach for acute and chronic forms of ocular allergies starts with allergen identification, followed by non-pharmacological treatments (allergen avoidance and hygiene measures), progressing to pharmacological treatment.⁷ Early detection of allergic triggers by skin testing and simple allergen avoidance measures, such as eyewear barrier protection, frequent washing of clothes, hypoallergenic bedding and bathing or showering before bedtime, may all help to stop disease progression.³ Avoidance of eye rubbing, cold compresses, and refrigerated artificial tears may also provide symptomatic relief.³ Contact lens wearers sensitized to pollen may be better served by switching to glasses during peak pollen seasons.³ Contact lenses must be removed during the administration of topical medications because of potential interaction between contact lenses and preservatives in ophthalmic medications but may be replaced after 10 minutes after administration.³

According to guidelines, topical medications are recommended treatments for the management of SAC and PAC.⁷ These medications are presented in **Table 2**. When symptoms of allergic rhinitis are present, treatment options usually include systemic antihistamines and intranasal corticosteroids in addition to topical ophthalmic treatment.⁷ Topical antihistamines (pheniramine, cetirizine) relieve itching and redness.³ Ocular decongestants (naphazoline, tetrahydrozoline) reduce ocular erythema through vasoconstriction but have little effect on alleviating itching.³ Ocular decongestants may be combined with antihistamines to relieve redness and itching, and these combination products are available over the counter without a prescription. The long-term use of ocular decongestants is limited by adverse effects such as ocular burning, mydriasis, worsening of narrow angle glaucoma, rebound hyperemia, conjunctivitis medicamentosa, and tachyphylaxis.³ Caution should be used with ocular decongestants in patients with cardiovascular disease, hyperthyroidism, and diabetes, and they should be avoided altogether in patients with angle closure glaucoma.³ Mast cell stabilizers inhibit degranulation of mast cells and prevent the release of mast cell mediators associated with the late phase of the allergic response.³ The mast cell stabilizer, cromolyn, requires a preloading period before exposure to allergens, generally 3 to 5 days but up to 2 weeks for full benefits of therapy, and frequent instillation, often leading to poor adherence to therapy.³

Dual-action drugs have antihistamine and mast cell stabilizing properties and are currently the most commonly prescribed group of agents for SAC.⁷ This combination of two mechanisms rapidly affects the early, as well as the late, phase of allergic conjunctivitis signs and symptoms.⁴ These agents block the histamine receptor, regulate mast cell reaction, and suppress the inflammatory mediator secretions.⁴ The antihistaminic effect reduces the early phase of ocular allergic response action such as itching, whereas the stabilization of mast cell inhibits the release of inflammatory mediators such as cytokines and lipid mediators, which is associated with the late-phase response of ocular allergic conjunctivitis.⁴ Side effects are generally mild and include headache, cold-like symptoms, burning, stinging, and possible transient dysgeusia (bitter taste).⁷

Table 2. Ocular Medications by Pharmacologic Classification^{8,9}

Medication (BRAND NAME)	OTC or Rx	Dosing	Minimum Age
Decongestants (Vasoconstrictors)			
Naphazoline	OTC	1-2 drops 4 times a day	6 years
Tetrahydrozoline	OTC	1-2 drops 4 times a day	6 years
Decongestant/Antihistamine			
Naphazoline/Pheniramine (NAPHCON A, OPCON-A, VISINE-A)	OTC	1-2 drops 4 times a day	6 years
Antihistamine			
Cetirizine (ZERVATE)	Rx	1 drop twice a day	2 years
Dual Action: Antihistamine/Mast Cell Stabilizers			
Alcaftadine (LASTACFT)	OTC	1 drop once daily	2 years
Azelastine (OPTIVAR)	Rx	1 drop twice a day	3 years
Bepotastine (BEPREVE)	Rx	1 drop twice a day	2 years
Epinastine (ELESTAT)	Rx	1 drop twice a day	2 years
Ketotifen (ALAWAY, ZATIDOR)	OTC	1 drop twice a day	3 years
Olopatadine 0.1% (PATANOL)	OTC	1 drop twice a day	2 years
Olopatadine 0.2% (PATADAY)	OTC	1 drops once a day	2 years
Olopatadine 0.7% (PATADAY)	OTC	1 drops once a day	2 years
Mast Cell Stabilizer			
Cromolyn (OPTICROM)	OTC	1-2 drops 4 to 6 times a day	4 years
Abbreviations: OTC = over the counter; Rx = prescription			

A summary of relevant drug information is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits

used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane: Treatments for Allergic Conjunctivitis¹

A 2015 Cochrane review assessed the efficacy of topical antihistamines and mast cell stabilizers, alone or in combination, in treating seasonal allergic conjunctivitis.¹ Literature was searched through July 14, 2014.¹ Thirty trials (n=4344) with 17 different drugs or treatment comparisons met inclusion criteria.¹ The primary outcome was any participant-reported evaluation (by questionnaire) of severity of 4 main ocular symptoms: itching, irritation, watering eye, and photophobia, both separately and, if possible, by an overall symptom score.¹ The following antihistamines and mast cell stabilizers marketed in the United States were evaluated in at least one RCT: olopatadine, ketotifen, azelastine, bepotastine, and combination of levocabastine and pemirolast.¹ The most common comparison was azelastine versus placebo (9 studies).¹ The quality of the studies and reporting was variable, but overall, the risk of bias was low.¹ Trials evaluated only short-term effects, with a range of treatment of one to eight weeks.¹ Meta-analysis was only possible in one comparison (olopatadine versus ketotifen).¹

Nine studies compared azelastine against placebo, conducted over 2 to 6 weeks.¹ All studies reported less itching with azelastine compared to placebo, but in some studies, it was not possible to confirm whether the results were statistically significant.¹ It was not possible to perform formal meta-analyses for this treatment comparison due to variations of outcomes reported and the lack of suitable data.¹

Four eligible studies compared olopatadine 0.1% and ketotifen 0.25% or 0.5%.¹ Studies were conducted over 2 to 4 weeks.¹ In all studies, the sample size was relatively small (n=32 to 92).¹ All four studies collected data on participant-reported itching using a 0-3 scale.¹ Two studies did not find any differences between olopatadine and ketotifen in itching reporting while two studies found a greater reduction in itching with olopatadine than with ketotifen after 2 weeks of treatment.¹ A random-effects meta-analysis of these 4 studies showed evidence of a statistically significant difference in favor of olopatadine in the reduction of itching at 14 days (mean difference [MD] -0.32, 95% confidence interval [CI], -0.59 to -0.06).¹ However, there was high statistical heterogeneity ($I^2 = 83\%$).¹

One study, at high risk of bias, compared bepotastine to olopatadine 0.2% in an investigator-masked, single-center, cross-over study that randomized 30 participants.¹ Participants were not masked.¹ The duration of treatment was 2 weeks, followed by a 7-day washout period.¹ After the washout period, participants were crossed-over to the alternative treatment for 2 additional weeks.¹ From the participants' diary responses, bepotastine was significantly more effective at relieving morning and evening ocular allergy symptoms ($P=0.032$ and $P<0.0001$, respectively) compared to olopatadine.¹

In summary, there is some evidence to support the ability of azelastine to reduce symptoms and signs of seasonal allergic conjunctivitis when compared with placebo.¹ There were limited data to evaluate whether some treatments are more effective than others for short-term symptom relief.¹ Results from a meta-analysis suggested that olopatadine may be more effective than ketotifen in relieving itching, although there was high statistical heterogeneity between the 4

studies.¹ The overall quality of the studies and reporting was poor, and most studies had small sample sizes.¹ Trials only evaluated short-term effects, with a range of treatment of one to eight weeks.¹

Topical Olopatadine in the Treatment of Allergic Conjunctivitis

A 2105 systematic review and meta-analysis assessed the safety and efficacy of topical olopatadine versus placebo and other topical medications in treating allergic conjunctivitis.² Literature was searched through January 4, 2015 and 23 RCTs met inclusion criteria.² Seventeen studies compared topical olopatadine with placebo, of which 11 included only adults and 6 included both adults and children.² Five studies compared the efficacy of topical olopatadine versus topical ketotifen, 5 compared topical olopatadine with epinastine, and 3 compared topical olopatadine with alcaftadine.² Overall, there was low risk of bias in the RCTs.² Ocular itching ratings were made on a scale of 0 (none) to 4 (severe), allowing half-unit increments.²

In the meta-analysis of olopatadine 0.1% or 0.2% versus placebo RCTs, olopatadine use was associated with a significantly lower ocular itch, with a pooled mean difference of -1.33 (95% CI, -1.43 to -1.23; $p < 0.00001$; $I^2 = 85\%$; 17 RCTs).² In the meta-analysis of olopatadine versus epinastine RCTs, no significant differences were identified between treatments in terms of ocular itch (MD -0.23; 95% CI, -0.50 to 0.03; $p = 0.08$; $I^2 = 91\%$; 5 RCTs).² Similar results were observed in the meta-analysis of olopatadine versus ketotifen 0.1% (MD -0.25; 95% CI, -0.64 to 0.15; $p = 0.22$; $I^2 = 91\%$; 5 RCTs).¹⁰ In the meta-analysis of olopatadine versus alcaftadine RCTs, alcaftadine use was associated with a significantly lower ocular itch, with a pooled MD of 0.39 (95% CI, 0.28 to 0.50; $p < 0.00001$; $I^2 = 0\%$; 3 RCTs).²

In summary, moderate-quality evidence confirms topical olopatadine 0.1% or 0.2% ophthalmic solution to be a safe and effective medication for allergic conjunctivitis in reducing ocular itch compared to placebo.² Moderate-quality evidence showed olopatadine has similar efficacy ketotifen and epinastine in relieving ocular itch.² Alcaftadine appears to have a superior effect in reducing ocular itch compared to topical olopatadine (moderate-quality evidence).² There was wide variation in study designs, inclusion criteria, baseline symptoms and signs, which made the meta-analysis difficult to interpret due to the heterogeneities across studies.²

After review, 8 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).¹⁰⁻¹⁷

Guidelines:

High Quality Guidelines: None identified.

After review, 2 guidelines were excluded due to poor quality.^{18,19}

Randomized Controlled Trials:

A total of 98 citations were manually reviewed from the initial literature search. After further review, 98 citations were excluded because of wrong study design (e.g, observational), comparator (e.g, no control or placebo-controlled), or outcome studied (e.g, non-clinical).

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Appendix 1: PDL Status

Generic	Brand	Route	Form	PDL	OTC
alcaftadine	LASTACRAFT ONCE DAILY RELIEF	OPHTHALMIC	DROPS	N	O
azelastine HCl	AZELASTINE HCL	OPHTHALMIC	DROPS		F
bepotastine besilate	BEPOTASTINE BESILATE	OPHTHALMIC	DROPS		F
bepotastine besilate	BEPREVE	OPHTHALMIC	DROPS		F
brimonidine tartrate	LUMIFY	OPHTHALMIC	DROPS		O
brimonidine tartrate/PF	LUMIFY	OPHTHALMIC	DROPERETTE		O
cetirizine HCl	ZERVIAE	OPHTHALMIC	DROPERETTE		F
cromolyn sodium	CROMOLYN SODIUM	OPHTHALMIC	DROPS		F
epinastine HCl	EPINASTINE HCL	OPHTHALMIC	DROPS		F
ketotifen fumarate	ALAWAY	OPHTHALMIC	DROPS		O
ketotifen fumarate	CHILDREN'S ALAWAY	OPHTHALMIC	DROPS		O
ketotifen fumarate	EYE ITCH RELIEF	OPHTHALMIC	DROPS		O
ketotifen fumarate	KETOTIFEN FUMARATE	OPHTHALMIC	DROPS		O
ketotifen fumarate	ZADITOR	OPHTHALMIC	DROPS		O
naphazoline HCl/glycerin	MAX REDNESS RELIEF	OPHTHALMIC	DROPS		O
naphazoline HCl/glycerin	REDNESS RELIEF	OPHTHALMIC	DROPS		O
naphazoline HCl/zinc sulfate	CLEAR EYES ACR	OPHTHALMIC	DROPS		O
olopatadine HCl	ADVANCED EYE RELIEF	OPHTHALMIC	DROPS		O
olopatadine HCl	EYE ALLERGY ITCH RELIEF	OPHTHALMIC	DROPS		O
olopatadine HCl	EYE ALLERGY ITCH-REDNESS RLF	OPHTHALMIC	DROPS		O
olopatadine HCl	OLOPATADINE HCL	OPHTHALMIC	DROPS		F
olopatadine HCl	OLOPATADINE HCL	OPHTHALMIC	DROPS		O
olopatadine HCl	PATADAY ONCE DAILY RELIEF	OPHTHALMIC	DROPS		O
olopatadine HCl	PATADAY TWICE DAILY RELIEF	OPHTHALMIC	DROPS		O
tetrahydroz/dext 70/peg 400/pv	EYE DROPS	OPHTHALMIC	DROPS		O
tetrahydroz/dext 70/peg 400/pv	EYE DROPS ADVANCED RELIEF	OPHTHALMIC	DROPS		O
tetrahydroz/dext 70/peg 400/pv	EYE DROPS MOISTURIZING RELIEF	OPHTHALMIC	DROPS		O
tetrahydrozoline HCl	EYE DROPS	OPHTHALMIC	DROPS		O
tetrahydrozoline HCl	MURINE PLUS	OPHTHALMIC	DROPS		O
tetrahydrozoline HCl/zinc sulf	EYE DROPS IRRITATION RELIEF	OPHTHALMIC	DROPS		O
tetrahydrozoline HCl/zinc sulf	EYE DROPS SEASONAL RELIEF	OPHTHALMIC	DROPS		O
tetrahydrozoline/polyethyl gly	EYE DROPS	OPHTHALMIC	DROPS		O
tetrahydrozoline/zinc/peg 400	MULTI-SYMPTOM RELIEF EYE	OPHTHALMIC	DROPS		O

Appendix 2: Specific Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics^{8,9}

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Naphazoline	Alpha ₁ Agonist, Vasoconstrictor	N/A	N/A	Onset of action: 10 minutes Duration: 2-6 hours
Tetrahydrozoline		N/A	N/A	Onset of action: 10 minutes Duration: 4-8 hours
Cetirizine	Histamine H ₁ Antagonist	N/A	N/A	Half-life: 8 hours Onset of action and Duration: N/A
Alcaftadine	Direct H ₁ -receptor antagonist and inhibitor of histamine release from mast cells	Minimal systemic absorption following ophthalmic administration	Metabolism: Primarily via aldehyde oxidation to the active major metabolite, carboxylic acid	Half-life: 2 hours (carboxylic acid) Onset of action: 15 minutes Duration: 3 hours
Azelastine			Metabolism: Primarily by CYP enzymes	Half-life: 2 hours Onset of action: 3 minutes Duration: 8 hours
Bepotastine			Metabolism: Minimal via CYP enzymes Excretion: Urine (75% to 90% unchanged drug)	Half-life: hours Onset of action: 3 minutes Duration: 16 hours
Epinastine			Protein Binding: 64% Metabolism <10% metabolized Excretion: IV: Urine (55% as unchanged drug; 30% feces	Half-life: 12 hours Onset of action: 3-5 minutes Duration: 8 hours
Olopatadine			Excretion: Urine (60% to 70% unchanged drug)	Half-life: 3 hours Onset of action: N/A Duration: N/A
Cromolyn	Mast Cell Stabilizer	Minimal systemic absorption following ophthalmic administration	Not known	Half-life: N/A Onset of action: N/A Duration: N/A
Abbreviations: CYP = cytochrome P450; N/A: Not Available				

Use in Specific Populations:

Contact lens wearers: Some products may contain benzalkonium chloride which may be absorbed by contact lenses; do not wear contact lenses during treatment.⁸

Table 2. Summary of Warnings and Precautions^{8,9}

Warning/Precaution	Naphazoline	Tetrahydrozoline
Use with caution in diabetes	X	X
Use with caution in narrow angle glaucoma	X	X
Use with caution in hyperthyroidism	X	X
Use with caution in cardiovascular disease	X	X

Other ophthalmic products used to treat allergic conjunctivitis do not have warnings or precautions.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to October 30, 2025>

1	Conjunctivitis, Allergic/ or alcaftadine.mp. or Olopatadine Hydrochloride/	4100
2	azelastine.mp.	853
3	Ophthalmic Solutions/ or bepotastine.mp.	16480
4	Brimonidine Tartrate/	1637
5	Cetirizine/ or cetirizine.mp.	2267
6	Cromolyn Sodium/	4144
7	Cromolyn Sodium/	4144
8	Anti-Allergic Agents/ or Conjunctivitis, Allergic/ or epinastine.mp.	12705
9	Ketotifen/	1197
10	Naphazoline/	400
11	Olopatadine Hydrochloride/	318
12	Ophthalmic Solutions/ or tetrahydrozoline.mp.	16518
13	Conjunctivitis, Allergic/	3883
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	37492
15	13 and 14	3883
16	limit 15 to (english language and humans)	3052
17	limit 16 to (clinical trial, phase iii or guideline or meta-analysis or practice guideline or "systematic review")	98



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Drug Use Research & Management Program
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Orphan Drug Evaluation: Elamipretide

Date of Review: February 2026

Generic Name: Elamipretide

End Date of Literature Search: 10/31/25

Brand Name (Manufacturer): FORZINITY (Stealth BioTherapeutics Inc)

Estimated Yearly Cost: \$793,520

Dossier Received: no

Purpose for Review:

- To review evidence of safety and effectiveness of elamipretide in people with Barth Syndrome and
- To establish prior authorization (PA) criteria to support medical appropriateness and necessity.

Plain Language Summary:

- Barth Syndrome is an inherited condition that decreases muscle strength, leads to heart failure, and increases risk of infection. There is no cure; treatment focuses on maintaining muscle function and managing symptoms such as tiredness, shortness of breath, or infections.
- In 2025, the Food and Drug Administration (FDA) approved a new medicine called elamipretide to improve muscle strength in people with Barth Syndrome.
- In 12 people with Barth Syndrome, elamipretide did not improve walking distance or tiredness compared to placebo (or sugar pill) over 12 weeks. Placebo also had similar benefit compared to elamipretide for outcomes of muscle strength, balance, time required to stand, overall disease improvement, and heart imaging at 12 weeks. This study enrolled people over 12 years of age who had mild or moderate motor function impairment. People with more severe disease and rapidly progressing symptoms were not included in the study.
- The Drug Use Research and Management group recommends that Oregon Health Authority only pay for elamipretide when other therapies available for symptoms of Barth Syndrome have been prescribed such as medicines to treat heart failure.

Research Questions:

1. What is the effectiveness and safety of elamipretide in people with Barth Syndrome?
2. Are there subpopulations based on age, symptom severity, type of heart failure, for which elamipretide is more effective or safe?

Conclusions:

- Elamipretide has no impact on motor function, heart failure symptoms, or fatigue in people with Barth Syndrome over 12 weeks (insufficient certainty evidence). A small randomized controlled trial (RCT) in 12 patients demonstrated no benefit in the 6-minute walk test (6MWT) or fatigue severity compared to placebo at 12 weeks.¹ There is no randomized controlled data evaluating elamipretide for longer than 12 weeks in people with Barth Syndrome, and observational data is significantly limited by lack of an adequate control group and high risk of bias.

Author: Sarah Servid, PharmD

- There is insufficient evidence for safety of elamipretide in patients with Barth syndrome. The majority of long-term safety data comes from an open-label, uncontrolled, extension study in 10 patients over 3 years.² The most common side effects were injection site reactions (e.g., erythema, pruritus, injection-site pain).
- There is no data on specific populations of patients with Barth Syndrome who may benefit from therapy with elamipretide. There is insufficient evidence for use of elamipretide in other conditions.

Recommendations:

- Implement prior authorization for elamipretide to require documentation of genetic testing and supportive care for heart failure.

Background:

- Barth Syndrome is an X-linked mitochondrial disease caused by mutations in the TFAZZIN (or TAZ) gene, an enzyme necessary for normal mitochondrial functioning. Common symptoms of Barth Syndrome include cardiomyopathy, skeletal muscle weakness or myopathy, delayed growth and cyclic neutropenia.³ Other complications can include arrhythmias, prolonged QT intervals, and developmental delay.³ Cardiomyopathy generally develops before the age of 5 years and is the most common cause of early mortality.^{4,5} Risk of early mortality appears to be highest in the first few years of life; patients that survive into their teenage years typically have normal systolic function.^{2,3} Advances in heart failure management have been correlated with improved mortality over time.⁵
- Current therapies focus on management of symptoms including heart failure related to cardiomyopathy and infection risk related to neutropenia.⁶ Because Barth Syndrome is a rare condition, much of the direct evidence for treatments is based on case series, observational studies, and small trials.⁶ There is very limited evidence from small observational studies (enrolling fewer than 20 people) that routine strength training or exercise may improve muscle function in people with Barth Syndrome.^{7,8} In 2017, the American Heart Association in 2017 recommended the following treatments for people with neuromuscular disorders and cardiac involvement:⁵
 - Angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) and beta adrenergic blockade for people with reduced ejection fraction (Class I; Level of Evidence B).⁵ Level B evidence includes data from a single RCT or non-randomized studies.
 - Diuretics to achieve a euvolemic state in patients with fluid retention associated with ventricular dysfunction (Class I; Level of Evidence C).⁵ Level C evidence is based on expert opinion, case studies or standard of care.
 - Aspirin or low-dose anticoagulation may be considered for people with Barth Syndrome and noncompaction phenotype (Class IIb; Level of Evidence C).
 - Thrombosis prophylaxis in the setting of normal systolic ventricular function and atrial fibrillation or flutter (Class IIb; Level of Evidence C).⁵
- In 2022, the American College of Cardiology issued the following recommendations for people with heart failure with preserved ejection fraction (HFpEF).⁹ No specific recommendations were issued for people with neuromuscular disorders.
 - Sodium-Glucose Cotransporter-2 inhibitors (SGLT2i) can be beneficial in decreasing heart failure hospitalizations and cardiovascular mortality (moderate strength recommendation based on moderate quality evidence from randomized trials).⁹
 - Titrate medications to manage hypertension and prevent morbidity (strong recommendation based on limited data from randomized or nonrandomized studies) and manage atrial fibrillation to improve symptoms (moderate strength recommendation based on expert opinion).⁹
 - Mineralocorticoid receptor antagonist (MRAs), ARB, and angiotensin receptor/neprilysin inhibitor (ARNi) may be considered to decrease hospitalizations, particularly among patients with left ventricular ejection fraction on the lower end of this spectrum (weak strength recommendation based on moderate quality data from randomized trials).⁹

- Estimated frequency of diagnosis:
 - As an X-linked genetic disorder Barth Syndrome is more common in males.
 - Literature estimates vary and this condition may be underdiagnosed.
 - Estimated incidence: 1 in 300,000 to 400,000 births.¹⁰
 - Estimated prevalence: 1 in 1 million males.² Estimates of individuals affected in the United States range from 111 to 150 people.^{10,11}
 - In Oregon Medicaid, 30 fee-for-service (FFS) and coordinated care organization (CCO) members had medical claims with a diagnosis of Barth Syndrome (ICD-10 code of E78.71) from 04/01/2024 to 03/31/2025. Claims estimates are likely inaccurate as many of these members also identified as female which is not consistent with an X-linked disease like Barth Syndrome which predominantly affects males.
- Diagnostic criteria:
 - The only definitive method to diagnose Barth Syndrome is genetic testing based on a pathogenic mutation in the TAZ gene.
 - 90% of patients with Barth Syndrome have cardiomyopathy.
- Outcome assessments:
 - The 6MWT measures distance walked over 6 minutes and evaluates both function and endurance. In healthy children and adolescents, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.^{12,13} In natural history studies of children and adolescents with Barth Syndrome, the average distance walked was 62% of the predicted value for matched cohorts with average values between 300 and 400 meters.⁸ Distance walked was generally smaller for adults compared to children and adolescents.⁸ A minimum clinically important difference for patients with Barth Syndrome has not been established in the literature. In Duchenne Muscular Dystrophy, a neuromuscular disorder that also causes skeletal muscle weakness and heart failure, an improvement of 30 meters has been documented as a clinically meaningful change.¹⁴
 - Total fatigue score based on the Barth Syndrome Symptom Assessment (BTHS-SA) includes 3 questions that evaluated fatigue at rest, fatigue during activities, and muscle weakness during activities.¹¹ Each question was scored on a 1 to 5 scale with higher scores indicating more severe symptoms. Total scores ranged from 3 (no symptoms) to 15 (severe symptoms).¹¹

Drug Information

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Elamipretide was approved by the FDA through the accelerated approval pathway based on results from a secondary outcome (muscle strength of the knee extensors) in an uncontrolled phase 2 extension study. Elamipretide is thought to work by improving the function of mitochondria in muscle cells.

Clinical Efficacy and Safety:

Clinical trials used to support FDA approval are described and evaluated below in **Table 2**.

Noteworthy trial design and patient characteristics include:

- Key inclusion criteria:
 - Pathogenic genetic variant in the TAZ gene (genetically confirmed Barth syndrome)
 - Ambulatory with impairment in the 6MWT as assessed by the provider. A specific definition of impairment was not documented.
 - At least 12 years of age and weighing more than 30 kg.

- Key exclusion criteria:
 - Hospitalization within 30 days or likely to need hospitalization during the trial.
 - Uncontrolled hypertension >160/100 mmHg, history of heart transplant or on the waiting list for transplant, or implantation of cardioverter defibrillator within previous 3 months.
- Baseline disease severity and population characteristics: Patients had generally mild to moderate symptoms with mean baseline 6MWT of 395 meters with BTHS-SA fatigue score of 8 (on a 3 to 15 scale with higher scores indicating greater severity) and preserved ejection fraction (EF 60%). Baseline treatments for heart failure symptoms and muscle strength were not reported.
- Number of participants: 12
- Trial outcomes evaluated at 12 weeks with subsequent long-term extension trial.

Efficacy:

- Primary outcomes: No difference from placebo in the 6MWT or total fatigue score on the BTHS-SA scale.¹ The study was powered to detect differences in these endpoints.
- Secondary outcomes: While not powered to detect differences in the secondary endpoints, none of the more than 10 secondary clinical outcomes (including knee extensor muscle strength) were different from placebo at 12 weeks.¹
- Exploratory outcomes in the long-term uncontrolled extension study: Ten patients (83%) were subsequently enrolled in a long-term extension study for an additional 168 weeks which provided the basis of FDA approval. In the long-term extension study, muscle strength of the knee extensors improved by a median of 34 Newtons after 12 weeks with subsequent increases of 35 to 68 Newtons over 3 years.¹¹ Outcomes are presented in **Table 1**. There is no established minimum clinically important difference for muscle strength in people with Barth Syndrome, and strength from a single muscle group has not been correlated with clinical functional outcomes.

Table 1. Exploratory outcomes of knee extensor muscle strength from the elamipretide trial¹¹

Visit timepoint	N	Elamipretide Median Newtons (range)	Placebo Median Newtons (range)
Screening	12	131 (77-210)	
Week 12 (controlled study)	12	124 (72-176)	126 (66-195)
Week 12 (open label extension)	10	166 (93-228)	NA
Week 168 (open label extension)	8	193 (155-235)	NA

Safety:

- Common adverse events included injection site reactions including erythema (100%), pain (75%), induration (67%), pruritus (67%), bruising (25%), and urticaria (25%).¹⁵ Similar adverse events have been reported in larger studies of elamipretide in other conditions.
- Four patients (33%) had discontinued treatment by week 36; in 2 cases discontinuation was related to hypersensitivity reactions.¹¹
- Elamipretide was associated with increased eosinophil counts which were highest 90 days after treatment initiation and had returned to baseline levels after 6-12 months.¹⁵
- Elamipretide has not been studied in people weighing less than 30 kg, and it is not approved for neonates because of risk for benzyl alcohol toxicity.¹⁵

Subgroup analyses and other populations:

- This study enrolled too few patients to determine if there are certain populations who may benefit from therapy.
- There is insufficient evidence that elamipretide has benefit in other conditions. Elamipretide has been studied in other types of mitochondrial diseases including a phase 3 study in patients with primary mitochondrial myopathy with no improvement in the 6MWT or total fatigue scores,^{16,17} in a phase 2 study of people with heart failure with reduced ejection fraction without improvement in left ventricular ejection fraction,¹⁸ and in people with myocardial infarction without improvement in short-term cardiac outcomes.¹⁹

Major evidence limitations (see **Table 2** for details):

- Unclear risk of selection, performance, and reporting bias during the 12-week randomized, crossover period.
- Risk of performance, detection, and attrition bias during the open-label, non-controlled extension period related to lack of blinding, lack of a control group, attrition, and effort-dependent outcome measures.
- Applicability concerns related to the population studied. Data is primarily applicable to adolescents and adults with mild to moderate functional impairment and fatigue.

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Reid Thompson, et al. 2020. ¹ FDA Integrated review ¹¹ NCT03098797 DB, PC, phase 2, single-site, crossover RCT	1. Elamipretide 40 mg SC daily 2. Placebo SC daily 12 week treatment period with 4 week washout before crossover to the alternative group. Patients could enroll in an open-label, non-controlled, extension study for up to 168 weeks.	<u>Demographics:</u> - Mean age 19.5 years - Race: White: 92% - 6MWT 395.5 m - BTHS-SA total fatigue: 8 - Mean EF: 60.6% - Median muscle strength (knee extensor): 131 (range 77-210) Newtons ¹¹ <u>Key Inclusion Criteria:</u> - Genetically-confirmed Barth syndrome - Age ≥ 12 years - Ambulatory with impairment in the 6MWT - Stable medication regimen for ≥ 30 days - Body weight >30 kg with eGFR ≥90 mL/min/1.73 m ² OR weight >40 kg with eGFR ≥60 mL/min/1.73 m ²	<u>ITT:</u> 12 <u>Attrition during 12 week RCT:</u> 0 <u>Attrition during 36 week extension:</u> 4 (33%)	<u>Primary Endpoint from baseline to 12 weeks:</u> Change in 6MWT 1. 43.0 m 2. 31.3 m Mean difference: 11.7m (95% CI -25.8 to 49.1); p=0.50 Median difference: -0.8 m (95% CI NR); p=0.97 Change in BTHS-SA total fatigue score 1. -1.4 2. -1.2 Mean difference -0.2 (95% CI -1.2 to 0.8); p=0.70 Median difference 0.06 (95% CI NR); p=0.89	NA	<u>DC due to adverse events:</u> 2 (17%) at week 12 related to injection site reactions	NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> UNCLEAR. Method of randomization was not reported. Baseline differences in mean age and BMI for people who received treatment-placebo (15.7 years and 18.23 kg/m ²) versus placebo-treatment (23 years and 16.88 kg/m ²). <u>Performance Bias:</u> UNCLEAR. Patient and study team were blinded with matching placebo; presence of injection site reactions may have resulted in unblinding. The extension period has high risk of bias related to lack of a control group or blinding particularly for effort-dependent outcomes like muscle strength and motor function tests. <u>Detection Bias:</u> LOW. Data management team and sponsor blinded to treatment with matching placebo. The open-label extension period has high risk of bias particularly for effort-dependent motor function and muscle strength. <u>Attrition Bias:</u> LOW. No attrition during the 12-week crossover period. High risk of bias for the extension period (33% discontinued treatment). <u>Reporting Bias:</u> HIGH. Data related to primary and secondary outcomes during the randomized crossover period was not reported. Outcomes during the non-controlled, extension period were emphasized. Study sponsor was involved with data analysis and writing the manuscript. <u>Other Bias:</u> UNCLEAR. Study funded by manufacturer. Cross-over design with adequate wash-out period between treatment periods based on expected drug duration.

		Key Exclusion Criteria: - Hospitalization within 30 days or likely to need hospitalization - Hypertension > 160/100 mmHg - History of heart transplant or on the waiting list for transplant - History of substance abuse - Implantation of cardioverter defibrillator within 3 months - Recent pubertal growth spurt - Current immuno-suppressive or chemotherapeutic drugs		Secondary Endpoint at 12 weeks: Change from baseline in muscle strength of knee extensors 1. 4 N 2. -5 N MD 6.7 Newtons; p=0.65 No difference from placebo in other secondary endpoints including: - 5-times sit-to-stand test - echocardiographic measurements - accelerometry counts - balance assessments - clinician, caregiver and patient global impression scales - other patient-reported fatigue and quality of life scales Specific outcome data was not reported.			Applicability: Patient: Exclusion criteria related to age, recent hospitalization, need for transplant, and ambulation would exclude patients with more severe or progressive disease. Barth Syndrome has primarily been associated with left ventricular dilation and reduced ejection fraction, but eligibility criteria based on age may select for people with preserved systolic function (mean EF 60%). Of enrolled patients 11 of 12 were White although Barth syndrome affects all ethnic groups. Intervention: The 40 mg dose was selected based on dosing in early studies of people with mitochondrial myopathy. However, subsequent trials in in mitochondrial myopathy have failed to demonstrate clinical benefit in the 6MWT. Standard of care interventions for heart failure, fatigue, or motor function were not described. Comparator: Placebo appropriate to determine efficacy. Data from the extension period lacks a comparator and does not control for potential confounding factors including patient growth or adjunct therapy. Outcomes: 6MWT, fatigue, and motor scales are appropriate to evaluate symptoms in a disease that commonly causes heart failure. 12 weeks is a relatively short period for a chronic, progressive disease. Cardiomyopathy is the leading cause of death in Barth syndrome and elamipretide does not appear to impact symptoms of heart failure. Setting: Single site (Johns Hopkins Hospital) beginning July 2017. The open-label extension was ongoing as of September 2020
Abbreviations: 6MWT = 6-minute walk test; ARR = absolute risk reduction; BTHS-SA = Barth Syndrome Symptom Assessment; CI = confidence interval; DB = double blind; DC = discontinue; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ITT = intention to treat; kg = kilogram; MD = mean difference; m = meters; mITT = modified intention to treat; mmHg = millimeters mercury; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous;							

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FORZINITY™ safely and effectively. See full prescribing information for FORZINITY.

FORZINITY (elamipretide) injection, for subcutaneous use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE

FORZINITY™ is a mitochondrial cardiolipin binder indicated to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg. (1)

This indication is approved under accelerated approval based on an improvement in knee extensor muscle strength, an intermediate clinical endpoint. (14) Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

For patients weighing 30 kg and greater, the recommended dosage is 40 mg subcutaneously once daily. (2.1)

Reduce the dose in adults with severe renal impairment. (2.2, 8.6).

DOSAGE FORMS AND STRENGTHS

Injection: 280 mg/3.5 mL (80 mg/mL) solution for injection in single-patient-use vials. (3)

CONTRAINDICATIONS

Serious hypersensitivity to any of the ingredients (4, 5.2)

WARNINGS AND PRECAUTIONS

- Benzyl alcohol toxicity: Do not use in neonates. (5.1)

ADVERSE REACTIONS

Most common adverse reactions are injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Stealth BioTherapeutics Inc. at 1-844-444-6486 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2025

Appendix 2: Proposed Prior Authorization Criteria

Elamipretide

Goal(s):

- Promote evidence-based standard of care in patients diagnosed with Barth Syndrome and with symptoms of cardiomyopathy and heart-related conditions.
- Limit to populations in which elamipretide has been studied and approved by the Food and Drug Administration.

Length of Authorization:

- Up to 12 months

Requires PA:

- Elamipretide

Covered Populations: FFS and CCO populations beginning 1/1/26 (pharmacy or provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Recommended adjunct treatments for heart-related conditions

Population	Adjunct treatment
Ejection fraction $\leq$ 40%	ACE inhibitor, ARB or angiotensin receptor/neprilysin inhibitor (ARNI) AND Beta blocker
Arrhythmias (atrial fibrillation or flutter) or non-compaction cardiomyopathy	Aspirin or anticoagulation
Current edema related to heart failure	Diuretics to achieve a euvolemic state (chronic or as needed)

Table 2. Target doses for Common HFrEF therapies

ACE inhibitor/ARB/ARNI	Target Dose	Beta Blockers	Target Dose
Candesartan	32 mg once daily	Bisoprolol	10 mg once daily
Captopril	50 mg three times daily	Carvedilol	25 mg twice daily
Enalapril	10 mg twice daily	Carvedilol CR	80 mg once daily
Fosinopril	40 mg once daily	Metoprolol	200 mg once daily
Lisinopril	20 mg once daily		

Losartan	50 mg once daily		
Quinapril	20 mg twice daily		
Ramipril	10 mg once daily		
Sacubitril-valsartan	97-103 mg twice daily		
Valsartan	160 mg twice daily		

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is there documentation of genetically-confirmed Barth Syndrome (e.g., pathogenic mutation in the TAZ gene)?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for a patient who weighs at least 30 kg?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Is the drug prescribed by a pediatric cardiologist or other specialist with experience in mitochondrial disorders?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Are there documented baseline assessments for all the following within the past year: • Cardiac function (e.g., ejection fraction) • Ambulatory motor function (e.g., 6MWT) • Muscle strength (e.g., physical therapy assessment)?	Yes: Go to #7	No: Pass to RPh. Deny; medical appropriateness
7. Is there documentation or provider attestation that the patient has impaired ambulatory function but is still able to complete a 6-minute walk test?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness
8. Is there documentation or provider attestation that medication therapy for heart failure has been optimized when appropriate (Table 1 and 2)?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is there documentation or provider attestation that a follow-up visit is scheduled with 4 weeks of initiation to assess tolerability and adherence?	Yes: Go to #10	No: Pass to RPh. Deny; medical appropriateness
10. Has the provider documented patient-specific goals for this therapy over the next 6 months? Note: Goals of therapy can vary from improvement in fatigue, motor function, quality of life disease, burden reduction, or disease stabilization.	Yes: Go to #11	No: Pass to RPh. Deny; medical appropriateness
11. Has the provider defined objective criteria to evaluate unsuccessful treatment or lack of response based on individual patient goals and current symptoms (i.e., when would the provider consider discontinuing therapy)? To qualify for treatment coverage, the patient and provider must have a documented discussion about when risks of the therapy outweigh the benefits and a knowledge of the realistic expectations of treatment efficacy. Care must always take place in the context of the patient's support systems, overall health, and core values.	Yes: Pass to RPh; Pend. Refer to DMAP for secondary review. Initial approval duration: 12 weeks	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence of adherence and tolerance to therapy based on claims history and provider assessment?	Yes: Go to #2	No: Pass to RPh. Deny; medical appropriateness
2. Has the provider re-evaluated the following baseline assessments within the past 2 months? • Motor function (e.g., 6MWT) • Muscle strength (e.g., physical therapy assessment)	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is there documentation that muscle strength has improved from baseline? Note: FDA-approval was based on improvements in knee extensor muscle strength after treatment over 12 weeks which continued to improve with over 3 years of follow-up.	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is there documentation that the patient's goals of therapy established prior to treatment have been met?	Yes: Pass to RPh; Pend. Refer to DMAP for secondary review. Approval duration: 12 months	No: Go to #5
5. Is there documentation that pre-established criteria for unsuccessful treatment or lack of response have been met?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #6
6. Have the patient and provider had a documented discussion about when benefits of the therapy outweigh the potential risks?	Yes: Pass to RPh; Pend. Refer to DMAP for secondary review. Approval duration: 12 months	No: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/26 (SS)
Implementation: TBD