Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, April 6, 2023 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. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	A. Gibler (OHA)
	E. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Oncology Prior Authorization Updates	
	B. Glaucoma Drugs Class Update & New Drug Evaluation	
	1. Public Comment	
	III. DUR NEW BUSINESS	
1:25 PM	A. Generalized Anxiety Disorder Update and Pregabalin Drug Use Evaluation	
	1. Generalized Anxiety Disorder MHCAG Algorithm	A. Gibler (OHA)
	2. Drug Use Evaluation/Prior Authorization Criteria	S. Servid (OSU)
	3. Public Comment	
	4. Discussion and Clinical Recommendations to OHA	
1:55 PM	B. Non-preferred Drugs in Select PDL Classes PA Update	D. Engen (OSU)
	1. Prior Authorization Criteria Update	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:05 PM	C. GLP-1 Receptor Agonists for Diabetes Policy Evaluation	M. Yokoyama (OSU)
	1. Policy Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	

IV. PREFERRED DRUG LIST NEW BUSINESS

2:25 PM	A. Tzield™ (teplizumab-mzwv) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:45 PM	B. Growth Hormone Focused Class Update for Adults 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	D. Engen (OSU)
3:05 PM	BREAK	
3:20 PM	C. Circadian Rhythm Sleep-Wake Disorders Indication Review 1. Indication Review/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
3:40 PM	D. Amyotrophic Lateral Sclerosis Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Relyvrio™ (sodium phenylbutyrate and taurursodiol) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
4:00 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Dental3	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2025
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2025
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2025

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 2nd, 2023 1:00 - 5:00 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; Pat DeMartino, MD; Douglas Carr, MD; Russ Huffman, PMHNP Cat Livingston, MD; Caryn Mickelson, PharmD; Robin Moody, MPH; Eriko Onishi, MD; Bill Origer, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Brandon Wells; Kyle Hamilton; Andrew Gibler, PharmD; Trevor Douglass, DC, MPH; Deborah Weston, JD; Amanda Parish

Audience: Mark Kantor, AllCare CCO; Carole Eisner, Novartis; Erin Nowak, AbbVie; Kevin Gallagher, Fennec Pharmaceuticals; **Zachariah Thomas, Axsome*;** YJ Shukla, EOCCO; Brain Howell, Novartis; Gary Paretneau, Dexcom; Chris Ferrin, IHN; Brandie Feger, Advanced Health CCO; Bill McDougal, Biogen; Lisa Ashton, J&J; Lori McDermott, Viking HCS; Michele Sabados, Alkermes; Mark Wolber, Sunovion; Jeremy Strand, Alexion; Shauna Wick; Dennis Murphy, Axsome; **Paul Thompson, Alkermes*;** Nic Vandersloot, Confederated Tribers of the Siletz; **Jamie Tobitt, Apellis***; **Lynda Finch, Biogen*;** Donald Nopper, Apellis; Georgette Dzwilewsk, Indivior; Matt Worthy, OHSU; Mariah Shoffner, APPE Student CIT; Tifffany Jones, PacificSource; Bill Eicholzer, Alexion; Susan Lakey Kevo, Janssen; Uche Mordi, BMS; Joni Fusick; **Erika Finanger; OHSU*;** Tiina Andrews, UHA; **Jared McPhail, Argenx*;** Jim Slater, CareOregon; Marc Rueckert, Argenx; Matt Metcalf, CSL Vifor; Michael Foster, BMS; Norm Navarro, Providence Health Plan; Rick Frees, Vertex Pharmaceutical; Saghi Maleki, Takeda; **Nirmal Ghuman, Janssen***

(*) Provided verbal testimony

Oregon Health Authority

OSU Oregon State University College of Pharmacy

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I. CALL TO ORDER

A. Roll Call & Introductions
- 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. Election of Chair and Vice-Chair
Dr. Ramirez volunteered to serve as Chair and Dr. DeMartino as Vice-Chair
ACTION: Motion to approve, 2nd, all in favor

D. Approval of Agenda and December 2022 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, all in favor with two abstentions

E. Department Update provided by Andrew Gibler, PharmD

F. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. Preferred Drug List (PDL) Old Business: Inhaled Anticholinergics
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

B. P&T Evidence Methods

C. P&T Operating Procedures

D. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Krazati® (adagrasib); Rezlidhia™ (olutasidenib); and Elahere™ (mirvetuximab soravtansine-gynx) to Table 1 in the Oncology Agents prior authorization (PA) criteria

E. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Xenpozyme™ (oplipudase alfa-rpcp) and Cuvrior™ (trientine tetrahydrochloride) based on FDA-approved labeling

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

III. DUR ACTIVITIES

A. Quarterly Utilization Report: Roger Citron, RPh

B. ProDUR Report: Lan Starkweather, PharmD

C. RetroDUR Report: Dave Engen, PharmD

D. Oregon State Drug Review: Kathy Sentena, PharmD
- **Antimicrobial Stewardship**
- **An Update in Lipid Lowering Therapies**
- **COVID-19 Vaccine Bivalent Boosters**

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IV. PREFERRED DRUG LIST NEW BUSINESS

A. GnRH Antagonists PA Update: Deanna Moretz, PharmD

Recommendations:

- Revise PA criteria for relugolix, estradiol, and norethindrone combination therapy to include management of moderate to severe pain associated with endometriosis in premenopausal women

ACTION: The Committee amended the proposed criteria to require a trial of at least three months' duration of first-line therapy in question #13

Motion to approve, 2nd, all in favor

B. Antidepressant Class Update: Kathy Sentena, PharmD; Andrew Gibler, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Update PA criteria for tricyclic antidepressants, esketamine and brexanolone as presented
- Evaluate costs in executive session

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

C. Spinal Muscular Atrophy DERP Report: Deanna Moretz, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Combine PA criteria for all 3 treatments into one with updates to clarify duration of therapy and FDA-approved age ranges
- Include pregnancy risk assessment for risdiplam

ACTION: The Committee amended the proposed criteria to remove the requirement that improvement be documented within one month of the renewal request

Motion to approve, 2nd, all in favor

D. Medications for Substance Use Disorders, Opioid & Alcohol:
Deanna Moretz, PharmD; Sarah Servid, PharmD

Recommendations:

- No PDL changes recommended based on review of recently published evidence
- Retire the PA criteria for lofexidine as there has been no utilization in the past year
- Update PA criteria to limit use of all long-acting opioids to patients who have inadequate pain relief with short-acting opioids

ACTION: The Committee recommended maintaining the safety edits present in the current long-acting PA criteria after amending to replace "pain contract" with "pain agreement" and allow up to 12-month renewal approvals for members established on

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treatment with no risk factors. The Committee also recommended requiring a taper plan for members new to the OHP for ongoing opioid treatment when their diagnosis is unfunded or if they have certain risk factors
Motion to approve, 2nd, all in favor

E. **Biologics for Rare Conditions Class Update:** Deanna Moretz, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Revise Ravulizumab PA criteria to include use and dosing guidance in adults with generalized MG who are anti-AChR antibody positive and add SC dosing recommendations for adults with PNH and aHUS
- Update PA criteria to support case by case review for members less than 21 years old with unfunded diagnosis, to evaluate whether medically appropriate and necessary

V. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Pat DeMartino, MD; Douglas Carr, MD; Russ Huffman, PMHNP Cat Livingston, MD; Caryn Mickelson, PharmD; Robin Moody, MPH; Eriko Onishi, MD; Bill Origer, MD

Staff Present: Sarah Servid, PharmD; Deanna Moretz, PharmD; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Lan Starkweather, PharmD; Brandon Wells; Andrew Gibler, PharmD

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Inhaled Anticholinergics**
Recommendation: Maintain Combivent Respimat® as preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **Antidepressant Class Update**
Recommendations: Make nefazodone preferred and make protriptyline & trimipramine voluntary non-preferred
ACTION: Motion to approve, 2nd, all in favor

C. **Biologics for Rare Conditions Class Update**
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

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VIII. ADJOURN

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Salem, Oregon 97301-1079

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

Generic Name	Brand Name
Elacestrant	ORSERDU
Mosunetuzumab-axgb	LUNSUMIO
Nadofaragene firadenovec-vncg	ADSTILADRIN
Pirtobrutinib	JAYPIRCA

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.

Length of Authorization:

- Up to 1 year

Requires PA:

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

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 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 or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5.

Approval Criteria		
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? Note: 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**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: 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:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #8
8. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #9
9. 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 #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
10. 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 03/06/2023)

New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
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
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA

Generic Name	Brand Name
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elacestrant	ORSERDU
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA

Generic Name	Brand Name
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mobecertinib	EXKIVITY
mosunetuzumab-axgb	LUNSUMIO
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
nivolumab; relatlimab-rmbw	OPDUALAG
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK

Generic Name	Brand Name
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
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
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE

Generic Name	Brand Name
zanubrutinib	BRUKINSA

Generic Name	Brand Name
ziv-aflibercept	ZALTRAP

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

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Drug Class Update with New Drug Evaluation: Glaucoma Drugs

Date of Review: April 2023

Date of Last Review: May 2018
Dates of Literature Search: 03/01/2018 - 01/13/2023
Brand Name (Manufacturer): Omlonti (Santen Inc)
Dossier Received: yes

Generic Name: omidenepag isopropyl

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: The purpose of this class update is to evaluate the literature for new evidence to inform the medical management of glaucoma and to analyze the comparative effectiveness and harms of a newly approved topical therapy for glaucoma called omidenepag.

Plain Language Summary:

- The reason for this review is to look at the information used to evaluate medications for the treatment of glaucoma to see if any changes to need to be made to the current policy.
- A review done by the Agency for Health Research and Quality found that the different types of eye drops used for the treatment of glaucoma are better than no eye drops for reducing the pressure in the eye that cause glaucoma. The review also looked at two newer eye drops, called netarsudil and latanoprostene, and found they worked as well as the eye drops that have been available longer, such as latanoprost and timolol, but were also associated with more unwanted side effects of the eye.
- A review done by the Canadian Agency for Drugs and Technologies in Health reviewed a class of eye drops used for glaucoma called prostaglandins. They found that all the prostaglandin eye drops worked about the same, except for bitmatoprost, which worked a little better than the others. Side effects were similar for all of these types of eye drops.
- Another type of medication used for glaucoma is called netarsudil and it was recently reviewed by the Cochrane Database for Systematic Reviews and found that this type of eye drop was better than saline drops at reducing pressure in the eye. It was not found to be better than two other drugs that are commonly used for glaucoma, called timolol and latanoprost.
- An organization that provides guidelines, called the National Institute for the Health and Care Excellence, updated their recommendations for the treatment of glaucoma support our current policy.
- A preservative-free eyedrop formulation of latanoprost (XELPROS) was recently approved by the Food and Drug Administration. A combination product containing latanoprost and netarsudil (ROCKLATAN) was also approved. Both medicines are used to reduce eye pressure in people with glaucoma.
- One new safety warning was issued by the Food and Drug Administration for betaxolol because it may reduce how fast the heart beats and lower blood pressure.

Author: Kathy Sentena, PharmD

- A newly approved eye drop by the Food and Drug Administration is called omidenepag. It was studied in people with glaucoma and high pressures in the eye, which found that it worked about as well as latanoprost and timolol, other drugs used for the same conditions.
- Based on this review, the Drug Use Research Management group recommends no changes to the current policy for the treatment of glaucoma.

Research Questions:

1. Are there comparative efficacy differences between glaucoma treatments based on outcomes such as intraocular pressure (IOP), loss of vison, or blindness?
2. Are there differences in harms between treatments for glaucoma that would have a clinical impact on patient care and should be factored into treatment decisions?
3. Are there subgroups of patients in which omidenepag would be safer or more effective than other available ophthalmic treatments for glaucoma?

Conclusions:

- New evidence for this review was available from 3 new systematic reviews and meta-analyses, one new guideline, 2 new formulations, one new safety alert and one new drug approval.
- A high quality systematic review and meta-analysis by Agency for Health Research and Quality (AHRQ) found that topical medications (e.g., beta-blockers, prostaglandins, alpha agonists and carbonic anhydrase inhibitors) were superior to placebo, or no treatment, in reducing IOP (mean difference [MD] -3.14 mm Hg; 95% confidence interval [CI], -4.19 to -2.08, I^2 = 95%) based on moderate quality of evidence.[1] Newer topical therapies, netarsudil and latanoprostene, were found to reduce IOP to a similar extent or slightly more than traditional topical agents for open-angle glaucoma (OAG) and ocular hypertension (OHT).[1] Netarsudil and latanoprostene were associated with more ocular adverse events compared to other topical medications.
- A Canadian Agency for Drugs and Technologies in Health (CADTH) review of ophthalmic prostaglandin analogues found no major differences in IOP lowering between the therapies; however, bitmatoprost was consistently shown to produce the most IOP lowering of all the therapies (moderate quality of evidence).[2] Adverse events (e.g., conjunctival hyperemia, keratitis, and follicular conjunctivitis) were found to be similar among the prostaglandins.
- A Cochrane review found that there was low quality evidence that netarsudil was more effective at lowering IOP than placebo (MD 3.11 mm Hg; 95% CI, 2.59 to 3.62). Timolol and latanoprost were found to be more effective at lowering IOP, MD 0.66 mm Hg and 0.97 mm Hg, respectively (low and moderate quality of evidence).[3]
- Updated guidance on the management of glaucoma by the National Institute for the Health and Care Excellence (NICE) supports the current Oregon Health Plan (OHP) policy for glaucoma therapies.[4]
- A preservative free version of latanoprost (XELPROS) and a combination product containing latanoprost and netarsudil (ROCKLATAN) were approved to reduce IOP in people with OAG and OHT.[5,6]
- One new safety alert was identified for betaxolol warning of minor decreases in heart rate and reduced blood pressure.[7]
- Omidenepag is a new prostaglandin analog used to lower IOP in people with OAG or OHT. Participants in the studies had a baseline IOP of 24-26 mmHg with low quality evidence demonstrating reductions at 3 months of 5.4 to 7.4 mmHg, which was noninferior to latanoprost once daily or timolol twice daily.[8] Common adverse events associated with the use of omidenepag are conjunctival hyperemia, photophobia, vision blurred, dry eye, instillation site pain, eye pain, ocular hyperemia, punctate keratitis, headache, eye irritation and visual impairment.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the current evidence.
- Maintain omidenepag as non-preferred on the PDL.

- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- The OHP provides coverage for glaucoma with the current policy preferring treatments from each class of therapies; miotics, alpha- adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues.
- The is no evidence of meaningful differences in efficacy/effectiveness within drug classes of ophthalmic medications used to treat glaucoma. Cost effectiveness and differences in harms data have been the driving forces for preferring specific therapies (**Appendix 1**). Newer fixed-combination products have not shown to provide substantial clinical benefit over the use of individual components.
- There are currently no prior authorization criteria for this class; however, utilization of PDL agents is high.
- There are approximately 1,700 Oregon Health Plan (OHP) fee-for-service (FFS) patients with a diagnosis of glaucoma with treatments having a minimal impact on overall OHP healthcare costs.

Background:

Glaucoma is a collection of eye diseases resulting from optic nerve damage that can lead to vision loss and blindness. Glaucoma is the second leading cause of blindness in the world.[9] Glaucoma is characterized by two variations: OAG and closed or narrow-angle glaucoma. A 2016 guideline estimates the incidence of OAG to be 2.2 million people in the United States, representing a 2% prevalence in adults.[10] The suggested incidence of narrow-angle glaucoma is 20 million people worldwide.[11] Open-angle glaucoma is more common in individuals of European and African decent and the incidence of narrow angle glaucoma is higher in people of Asian heritage. Risk factors for the development of open-angle glaucoma include: age, black race, family history, and elevated IOP. Hypertension and diabetes have also been associated with an increased risk of OAG. Risk factors for development of visual loss and progression to blindness are not fully known.[9] Risk factors for patients with angle-closure glaucoma are family history, age over 60 years, female, hyperopia (farsightedness), certain medications, race and pseudoexfoliation (age related systemic syndrome that effect the eye).

Open-angle glaucoma is a more chronic condition while narrow-angle glaucoma often occurs suddenly and is considered a medical emergency. Both types are a result of inadequate drainage of the eye causing IOP. Open-angle glaucoma causes peripheral visual field loss due to optic neuropathy. Open-angle glaucoma is often associated with elevated IOP levels and reduction in IOP is important to prevent the progression to loss of vision.[12] Elevated IOP is the result of increased aqueous production or decreased aqueous outflow. The increased pressure can result in “cupping” of the optic nerve causing loss of ganglion cell axons. The pathogenesis of OAG is not clear but thought to be a combination of circulatory or extracellular matrix factors, variation in axon susceptibility and systemic factors. If left untreated OAG can cause visual field loss and irreversible blindness.[9] Narrow-angle glaucoma is the result of narrowing or closure of the anterior chamber angle. This chamber is responsible for drainage of the aqueous humor, which is the fluid that fills the eyeball. Prevention of drainage from this pathway can cause increased IOP with subsequent damage to the optic nerve. Narrow-angle glaucoma is caused by certain anatomical traits of the eye. Acute blockage of the entire angle in narrow-closure glaucoma can cause rapidly rising IOP and subsequent vision loss and potential blindness if not treated. Chronic narrow-angle glaucoma can occur over time and result in scarring of the optic nerve.[9] Secondary glaucoma can be caused by uveitis, trauma, glucocorticoids, vasoproliferative retinopathy, or ocular syndromes (i.e., pigment dispersion or pseudoexfoliation).

The consensus for initiating treatment in patients with open-angle glaucoma are two IOP readings of more than 22 mmHg, with normal ranges of IOP being 8-21 mm Hg.[9] Treatment options for lowering IOP include medications, laser therapy or surgery; however, pharmacotherapy or laser are preferred. If medical treatment is used, prostaglandins (e.g., latanoprost, travoprost, bimatoprost) are recommended as the first-line based on once-daily dosing, improved efficacy and low incidence of side-effects compared to beta-blockers (e.g., betaxolol, carteolol, timolol), carbonic anhydrase inhibitors (e.g., brinzolamide, dorzolamide),

alpha adrenergic agonists (e.g., brimonidine, apraclonidine), Rho kinase inhibitors (RKi) (e.g., netarsudil) and nitric oxide-donating therapy (e.g., latanoprostene bunod).[1] Beta-blockers are commonly used as a second-line treatment option due to side effects such as bradycardia, worsening heart failure and increased airway resistance. Alpha adrenergic agonists have been shown to have similar efficacy to beta-blockers in lowering IOP but a higher incidence of ocular side effects prevents them from being an initial treatment option. Topical carbonic anhydrase inhibitors have been shown to be less effective than other options and are associated with burning, stinging and allergic reactions.[12] Miotics (e.g., pilocarpine) are associated with fixed, small pupils, myopia, and increased visual disturbances and are therefore not widely used. If monotherapy is not effective, combination therapy of beta blockers plus prostaglandin or beta blocker plus carbonic anhydrase inhibitor have been shown to lower IOP more than single therapy. Fixed-dose combination products are offered most commonly with timolol and an additional agent.[12]

Acute treatment of angle-closure glaucoma includes methods to lower quickly reduce IOP.[9] A regimen of topical ophthalmic drops consisting of a beta-blocker, an alpha agonist and treatment to produce miosis (i.e., pilocarpine) is often recommended. Systemic treatment with acetazolamide, mannitol or oral glycerol or isosorbide is also recommended. Once IOP is reduced, laser peripheral iridotomy is used to prevent future elevations of IOP. Peripheral iridotomy is the treatment of choice for patients with angle-closure glaucoma. Secondary angle-closure glaucoma is treated with removing the offending cause if possible and utilizing medications recommended for open-angle glaucoma if necessary.

Outcomes used to track response to therapy are IOP, visual field changes, condition of the optic nerve and progression to blindness.[10] The goal of treating open-angle glaucoma is to lower IOP to a level to prevent further eye damage. The magnitude of IOP lowering is dependent upon the degree of optic nerve damage, rate of progression, family history, age, and presence of disc hemorrhages.[10] There is no standard IOP target; however, IOP lowering of 25-30% (approximately 6-7 mmHg) below IOP at presentation has been suggested.[9,11,13] Evidence has shown that lowering IOP slows progression of visual impairment, and potential blindness associated with elevated IOP levels.

The overall cost per quarter for glaucoma medications in the fee-for-service (FFS) population is not significant. There is about 95% preferred drug utilization for the class. As expected, the highest utilization is within the prostaglandin class followed by alpha agonists.

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:

AHRQ – Screening for Glaucoma in Adults: A Systematic Review for the U.S. Preventative Task Force

In 2022 AHRQ evaluated the evidence for the management and treatment of glaucoma with literature updated through January 21, 2022.[1] There were 83 studies included in the review (n=75,887).[1] The mean age ranged from 61 to 66 years and females accounting for 50% to 68% of the participants. For the purpose of this update, the focus will be on new evidence related to the treatment of glaucoma. There were two key questions related to drug therapy: the effects of newer agents (e.g., netarsudil and latanoprostene bunod) compared to older therapies and the harms of newer therapies compared to older products.

There was moderate quality evidence from 16 trials (n=3,706) that topical medication (e.g., beta-blockers, prostaglandins, alpha agonists and carbonic anhydrase inhibitors) were superior to placebo, or no treatment, in reducing IOP (MD -3.14 mm Hg; 95% CI, -4.19 to -2.08, I^2 = 95%) (Table 1).[1] High heterogeneity reduces the confidence in these findings; however, the estimate of effect is precise. Topical medical treatment was associated with decreased risk of progression of vision loss compared to placebo (relative risk [RR] 0.68; 95% CI, 0.49 to 0.96; I^2 = 53%; moderate strength of evidence). Serious adverse events or withdrawals due to adverse events were similar between treatment and placebo (low quality of evidence).[1] Ocular adverse events (e.g., redness, burning, irritation, itching, tearing) were increased with topical medication compared to placebo based on two trials (RR 1.21; 95% CI, 1.10 to 1.33 and RR 3.52; 95% CI, 2.46 to 5.02; low quality of evidence).[1]

Table 1. Topical Medications compared to Placebo/No Treatment (pooled analyses)[1]

Drug Class	Number of Trials	N	Estimates (95% CI)	I^2
Beta-blockers	9	455	MD -3.75 (-5.43 to -2.06)	92%
Prostaglandins	1	516	MD -2.70 (-3.34 to -2.06)	NA
Alpha agonists	1	30	MD -2.30 (-3.52 to -1.08)	NA
Carbonic anhydrase inhibitors	4	1,635	MD -1.20 (-2.30 to -0.61)	0%
Mixed/various medications	1	817	MD -4.60 (-4.85 to -4.35)	NA
Abbreviations: MD = mean difference; NA = not applicable				

Moderate evidence demonstrated newer topical therapies, netarsudil and latanoprostene, reduced IOP by a similar margin or greater efficacy than older medications. Three fair quality trials, in participants with OAG and OHT, evaluated the effectiveness of netarsudil compared to timolol for the outcome of IOP lowering at 3 and 12 months.[1] Netarsudil was found to be noninferior to timolol. Comparative evidence from a pooled analysis of two trials found similar IOP lowering for netarsudil and latanoprost at 12 months. The likelihood of patients achieving an IOP of 18 mm Hg or less at 12 months was similar for netarsudil and latanoprost, 57.4% and 65.5%, respectively (RR 0.73; 95% CI, 0.61 to 0.88; $p<0.05$).[1] A trial evaluating latanoprostene found more IOP lowering, by a small amount (1.2 mm Hg) compared to latanoprost at 1 month. Latanoprostene bunod demonstrated greater reductions of IOP compared to timolol by a mean difference of -1.0 to -1.3 mm Hg (2 trials). An additional pooled analysis of latanoprostene compared to timolol found latanoprostene to have an increased likelihood of IOP equal to or less than 18 mm Hg, 20.2% and 11.2% (p=0.001) at 3 months.[1] When compared to timolol, netarsudil was associated with an increased risk of adverse ocular events and withdrawals due to adverse events, based on moderate evidence. Latanoprostene was associated with an increased risk of ocular events compared to timolol (RR 1.72; 95% CI, 1.22 to 2.42; moderate quality evidence) based on data from two pooled trials (n=840) .[1] Latanoprostene and latanoprost were associated with a similar risk of adverse events and withdrawals due to adverse events.

CADTH – Prostaglandin Analogues for Ophthalmic Use

The evidence for the use of prostaglandin analogues in adults to reduce IOP was the focus of a CADTH report. Bimatoprost monotherapy or in combination with timolol was compared to latanoprost (monotherapy or in combination with timolol), latanoprostene, travoprost (monotherapy or in combination with timolol) or tafluprost.[2] Thirteen publications met the inclusion criteria; 5 systematic reviews, 7 randomized controlled trials, and one cost-effectiveness analysis. Participants in the trials were adults (18 years or older and mean age of 31 to 64 years) diagnosed with glaucoma or glaucomatous conditions (e.g., primary open-angle glaucoma [POAG], OAG, OHT, normal tension glaucoma [NTG] and pseudo-exfoliative glaucoma [PXG]). Participants were both treatment naïve and treatment experienced. Trials were conducted in the United States (U.S,), China, Australia, Canada, and Japan.[2] Conflicts of interest were noted in one of the systematic reviews. Risk of bias for the systematic reviews was mixed, based on the authors' assessment. The included RCTs were found to be well representative of patients with glaucoma and while there were some issues with blinding and randomization, the overall study quality was fair. The primary outcome in all systematic reviews was change in IOP.

Bimatoprost, travoprost, latanoprost, and tafluprost were all associated with a 15% to 20% reduction in IOP, with no major delineation in clinical differences.[2] Three to six month pooled analysis data on the use of bimatoprost demonstrated more reduction in IOP compared to latanoprost and travoprost; with bitmatoprost having the greatest IOP lowering effect and latanoprost have the weakest effect.[2] The clinical effectiveness of the prostaglandin analogues on ocular pressure was determined to be similar by the authors. Ocular perfusion pressure, as an indirect measurement of vascular profusion of the posterior ocular segment that is linked to IOP, was measured and lowering was compared between the prostaglandin analogues. There were no statistically significant differences found between the bimatoprost and latanoprost/timolol for ocular perfusion pressure.

Adverse events were found to be similar between the prostaglandin analogues. The most common adverse events were conjunctival hyperemia, keratitis, and follicular conjunctivitis. One meta-analysis found that conjunctival hyperemia was more common with bimatoprost and travoprost when compared to latanoprost.[2]

Cochrane – Rho kinase Inhibitor for Primary Open-angle Glaucoma and Ocular Hypertension

Cochrane performed a systematic review and meta-analysis in 2022 to evaluate the comparative effectiveness and safety profile of RKi compared to placebo and other active treatments. Seventeen trials lasting up to 12 months met inclusion criteria.[3] Trials included adult participants (n=4953) with a diagnosis of OAG, POAG or OHT.[3] Rho kinase inhibitors, netarsudil and ripasudil (not available in the US), were studied as monotherapies or in combination with latanoprost or timolol and compared to placebo, latanoprost, timolol or netarsudil. The risk of bias was found to be low in seven trials, moderate in three trials and high in three.

Data from 3 RCTs (n=155) of netarsudil compared to placebo, netarsudil was found to lower IOP more than placebo (MD 3.11 mm Hg; 95% CI, 2.59 to 3.62; low quality evidence).[3] Low quality evidence from three trials (n=1415) found timolol to be superior to netarsudil by a MD of -0.66 mmHg (95% CI, 0.41 to 0.91). Latanoprost was also found to lower IOP more than netarsudil (MD 0.97 mm Hg; 95% CI, 0.67 to 1.27; moderate quality evidence).[3] Combination therapy of netarsudil and latanoprost was more effective than latanoprost monotherapy at lowering IOP, measured at 6 months, by a MD of 1.64 mm Hg (95% CI, 1.11 to 2.16) based on moderate quality evidence; however, there were more adverse events in the combination therapy group, 26 more per 100 person-months (low quality evidence).[3] There was moderate quality evidence that the combination of netarsudil in combination with latanoprost was more effective than netarsudil monotherapy (MD 2.66 mm Hg; 95% CI, 2.35 to 2.98) with a similar risk of adverse events. The combination of netarsudil and timolol was slightly more effective than timolol alone, a MD of 0.75 mm Hg (95% CI, 0.21 to 1.29) with more adverse reactions in the combination group, 35 more events per 100 person-months (moderate quality evidence for both).[3] Overall, RKi were not associated with any serious adverse events.

After review, thirteen systematic reviews were excluded due to poor quality (e.g., indirect 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).[14–17,18–25]

New Guidelines:
High Quality Guidelines:
NICE – Glaucoma: Diagnosis and Management
In 2022 NICE updated their 2017 recommendations for the treatment of glaucoma.[4] Treatment should be considered for people with OHT and an IOP of 24 mm Hg, if the patient is at risk of visual impairment in their lifetime and not a candidate for selective laser trabeculoplasty (SLT). Initial pharmacotherapy recommendations include the use of a generic prostaglandin analogue for people with OHT or chronic open-angle glaucoma (COAG). For those people who are unable to tolerate a prostaglandin analogue, another generic prostaglandin analogue should be considered. Beta-blockers are recommended as second line therapy. Other options include a non-generic prostaglandin, carbonic anhydrase inhibitor, sympathomimetic, miotic or a combination of therapies.[4] People with an IOP of 24 mm Hg or higher despite current therapy should be offered a medication from an alternate therapeutic class (e.g., beta-blocker, carbonic anhydrase inhibitor or sympathomimetic). Combination therapy of medications from different therapeutic classes may be needed to adequately reduce IOP. Preservative free eye drops should be reserved for people who have an allergy to preservatives or ocular surface disease which is considered clinically significant and are at high risk of conversion to COAG. Treatment is not recommended for those people with suspected COAG but have an IOP less than 24 mm Hg unless they are at risk of visual impairment.[4] Pharmacotherapy may be discontinued in people with OHT or suspected COAG if they have a low risk of becoming visually impaired and an acceptable IOP. If therapy is discontinued, reassessment of IOP should be done within one to four months. People who have had surgery and have COAG whose IOP has not been reduced to a level to prevent sight loss may consider pharmacological treatment, and potentially combination therapy from two different classes.[4]

After review, two guidelines were excluded due to poor quality or not applicable to the review.[13,26]

New Formulations or Indications:

New Formulations:
XELPROS (latanoprost ophthalmic emulsion 0.005%) – A new formulation of latanoprost ophthalmic emulsion was approved in September of 2018.[6] XELPROS is a prostaglandin F2alpha analog used to reduce IOP in people with OAG or OHT. It differs from other latanoprost products because it is not formulated with benzalkonium chloride (BAK), a commonly used preservative. Studies in participants with a baseline IOP of 23-26 mmHg demonstrated mean reductions of 6-8 mm Hg.[6] XELPROS is given once daily in the evening in the affected eye at 12 weeks.

ROCKLATAN (netarsudil/latanoprost) – A combination product containing a RKi and a prostaglandin F2α analogue (netarsudil 0.02% and latanoprost 0.005%) was approved in March 2019 for the use in people with IOP or OHT to reduce elevated IOPs.[5] ROCKLATAN was approved based on two randomized controlled trials (RCTs) which found the combination product to lower IOP 1-3 mm Hg more than the monotherapy components over 3 months.[5]

New FDA Safety Alerts:

Table 2. 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)
Betaxolol[7]	Betoptic S®	June 2021	Warning	Betaxolol has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S should be discontinued at the first signs of cardiac failure.

Randomized Controlled Trials:
A total of 140 citations were manually reviewed from the initial literature search. After further review all 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).

NEW DRUG EVALUATION:
See **Appendix 4** 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.

Clinical Efficacy:
Omidenepag is a prostaglandin analog approved in September of 2022 for the reduction of elevated IOP in patients with OAG or OHT.[27] Omidenepag works by being a relatively selective prostaglandin E2 (EP2) receptor agonist and is thought to increase uveoscleral outflow of aqueous humor. Omidenepag 0.002% solution is administered in the affected eye once a day at night.[27]

Omidenepag was approved based on 3, nonpublished, RCTs.[8] Due to the unavailability of published data, the evidence cannot be critically evaluated. Data in **Table 4** is based on the FDA Clinical Review.[8] All trials included participants with open-angle glaucoma or ocular hypertension with a baseline IOP of 24-26 mmHg.[8] Studies lasted 3 months. The primary endpoint was the non-inferiority (NI) of omidenepag compared to active treatment at month 3. For all studies, the non-inferiority was determined by the upper limit of the 2-sided 95% CI for the difference in the mean IOP of equal to or less than 1.5 mmHg at all 9 timepoints and equal to and less than 1.0 mmHg at a majority (5 or more) of the 9 timepoints. Secondary endpoints were considered exploratory.

The FDA concluded that compared to latanoprost 0.005% and timolol maleate 0.5% solution, changes in mean IOPs were not clinically significantly different with omidenepag; however, reductions in IOP obtained with omidenepag were considered clinically meaningful.[8] Reduction in mean IOPs from baseline were -6.0 mmHg for those treated with omidenepag compared to a reduction of -6.1 mmHg with timolol in one study (NI achieved) and -6.2 in the second study (NI not achieved). Omidenepag decreased mean IOPs by 6.5 mm Hg when compared to latanoprost which decreased IOPs by 7.0 mmHg (NI achieved).

Additional evidence includes four published trials. Three trials were excluded due to quality and study design; one was a dose -ranging phase 2 study (SPECTRUM-6), the second study was a small (n=26), single arm, open-label study in exclusively Japanese patients (FUJI) and the third study was an open-label, phase 3 study (RENGE) evaluating the durability of IOP reductions at 52 weeks but lacked statistical comparison between the groups.[28–30]

In a poor quality, phase 3 trial omidenepag was compared to latanoprost in a NI study enrolling 190 participants. Participants were included if they had a baseline IOP of 22 mm Hg or higher in at least one eye and 34 mm Hg or less in both eyes at 3 timepoints.[31] If both eyes met the criteria, then the eye with the higher mean diurnal IOP at baseline was used, if they were the same then the right eye was designated the study eye. The primary endpoint was the change in mean diurnal IOP from baseline to week 4. Noninferiority was determined if they upper limit of thee 95% CI was at or below the NI margin of 1.5 mm Hg. Reductions in IOP were similar between groups at 4 weeks. Omidenepag decreased mean IOP by -5.93 mm Hg and latanoprost reduced IOP by -6.56 mm Hg (MD 0.63 mm Hg; 95% CI, 0.01 to 1.26; P=0.048).[31] Omidenepag was found to be noninferior to latanoprost, with significantly less IOP lowering but the difference is unlikely to be clinically meaningful. Limitations to these findings include short trial duration, randomization and medication preparation that could lead to study drug unmasking, and lack of methodological details on study procedure.

Clinical Safety:
The most common adverse effects associated with the use of omidenepag in 1% or greater of the people treated are: conjunctival hyperemia, photophobia, vision blurred, dry eye, instillation site pain, eye pain, ocular hyperemia, punctate keratitis, headache, eye irritation and visual impairment.[27] There are warnings for the risk of pigmentation of the iris, which is often permanent, due to an increase in melanin content in the melanocytes. Pigmentation in the periorbital tissue and eyelashes are most likely reversible.[27] Eyelashes and vellus hair may be increased in length, thickness and in number which are most likely reversible upon discontinuation. Ocular inflammation and macular edema have also occurred with omidenepag use. There are no contraindications for the use of omidenepag.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) IOP reduction
2) Duration of IOP reduction
3) Visual field changes
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) IOP reduction at 3 months

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Omidenepag is a relatively selective E2 (EP2) receptor agonist which decreases IOP due to ocular hypotensive activity
Oral Bioavailability	Not applicable
Distribution and Protein Binding	Not applicable
Elimination	83% feces and 4% urine
Half-Life	Not described
Metabolism	Omidenepag isopropyl is rapidly metabolized in the eye to omidenepag by carboxylesterase-1 and further metabolized in the liver through oxidation, N-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation.

Abbreviations: IOP = intraocular pressure

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Study 01171505[8] Phase 3 MC, NI, RCT, SB	1. Omidenepag 0.002% solution once daily in the evening in the affected eye 2. Latanoprost 0.005% solution once daily in affected eye Study duration: 3 months	Demographics: Age: 54.6 years Male: 52.6% Asian: 100% Key Inclusion Criteria: - OAG or OHT Key Exclusion Criteria: - Not described	ITT: 1. 184 2. 185 PP: 1. 170 2. 177 Attrition: 1. 15 (8.1%) 2. 8 (4.3%)	Primary Endpoint: Diurnal IOP reduction IOP in the study eye at month 3 (Upper CI)*: 1. -6.5 mm Hg 2. -7.0 mm Hg LSMD 0.5 mm Hg (95% CI, -0.2 to 1.1) NI was achieved Secondary Endpoints: All secondary endpoints were considered exploratory	NA for all	Discontinuations due to adverse events: 1. 4 (2.2%) 2. 2 (1.1%) Conjuntiva hyperemia: 1. 18 (9.7%) 2. 7 (3.8%) Photophobia: 1. 6 (3.2%) 2. 1 (0.5%) Ocular hyperemia: 1. 3 (1.6%) 2. 2 (1.1%)	NA for all	**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results are most applicable to patients in their mid-fifties who are Asian. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: Latanoprost is an appropriate comparator. Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: India, Taiwan, Korea and Singapore
2. Study 011091N† SPECTRUM 3 Phase 3 DB, MC, RCT	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Timolol 0.5% twice daily in affected eye Study duration: 3 months	Demographics: Age: 64.1 years Male: 39.3% Asian: 0.9% White: 74.2% Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 212 2. 213 PP: 1. 189 2. 204 Attrition: 1. 22 (10.4%) 2. 11 (5.1%)	Primary Endpoint: IOP in the study eye at month 3 (Upper CI)*: 1. -6.0 mm Hg 2. -6.2 mm Hg LSMD 0.8 mm Hg (95% CI, 0.2 to 1.4) Did not meet NI criteria Secondary Endpoints: See above		Discontinuations due to adverse events: 1. 10 (4.7%) 2. 3 (1.4%) Conjuntiva hyperemia: 1. 10 (4.7%) 2. 7 (3.3%) Photophobia: 1. 9 (4.3%) 2. 1 (0.5%) Ocular hyperemia: 1. 5 (2.4%) 2. 3 (1.4%)		**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results are most applicable to people who are in their 60s and are White who have OAG or OHT. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: see above Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: See above

3. Study 0117101N†[8] SPECTRUM 4 DB, MC, RCT Phase 3	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Timolol 0.5% twice daily in affected eye Study duration: 3 months	Demographics: Age: 64 years Male: 89.5% Asian: 3.9% White: 64% Key Inclusion Criteria: - OAG, OHT and pediatric glaucoma Key Exclusion Criteria: - Not described	ITT: 1. 204 2. 205 PP: 1. 187 2. 196 Attrition: 1. 17 (8.3%) 2.9 (4.4%)	Primary Endpoint: IOP in the study eye at month 3 (Upper CI)*: 1. -6.0 mm Hg 2. -6.1 mm Hg LSMD 0.1 mm Hg (95% CI, 0.7 to -0.5) NI was achieved Secondary Endpoints: See above		Discontinuations due to adverse events: 1. 13 (6.4%) 2. 3 (1.5%) Photophobia: 1. 8 (3.9%) 2. 0 (0%) Ocular hyperemia: 1. 3 (1.5%) 2. 2 (1.0%)		**Risk of Bias (low/high/unclear)**: Not able to assess due to evidence not being published. **Applicability**: Patient: Results pertain mostly to White males in their 60s. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: Timolol is an appropriate comparator. Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: United States
4. Aihara[31] AYAME MC, NI, PG, RCT Phase 3	1. Omidenepag 0.002% once daily in the evening in the affected eye 2. Latanoprost 0.005% once daily in affected eye Study duration: 4 weeks	Demographics: Age: 63.6 years Male: 45% Asian: 100% Baseline IOP: 23.59 mmHg Prior use of IOP medications: 51.3% Key Inclusion Criteria: - Bilateral POAG or OHT - 20 years or older - Baseline IOP of 22 mm Hg or higher in at least one eye and 34 mm Hg or less in both eyes at 3 timepoints Key Exclusion Criteria: - Visual field depression that was severe or at risk of progression during the study - Corneal abnormality or other condition potentially	ITT: 1. 94 2. 96 PP: 1. 92 2. 95 Attrition: 1. 2 (2.1%) 2. 1 (1%)	Primary Endpoint: Change from baseline in mean diurnal IOP at week 4: 1. -5.93 mm Hg 2. -6.56 mm Hg MD 0.63 mm Hg (95% CI, 0.01 to 1.26) P=0.048 NI was met (the NI margin was 1.5 mmHg) Per Protocol Population: Change from baseline in mean diurnal IOP at week 4: MD 0.65 mm Hg (95% CI, 0.02 to 1.28) P=0.048		Discontinuations due to adverse events: 1. 2 (2.1%) 2. 2 (2.1%) Conjunctiva hyperemia: 1. 23 (24.5%) 2. 10 (10.4%) Photophobia: 1. 4 (4.3%) 2. 0 Overall drug adverse reactions: 1. 37 (39.4%) 2. 18 (18.8%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (high) Randomized 1:1 by the permuted block method by the study medication randomization manager who prepared study medication and medication codes. Performance Bias: (unclear) Investigators and observers were blinded but details not provided. Boxes for medications were the dame but eyedrop bottles were different. Detection Bias: (unclear) Not described. Attrition Bias: (low) Attrition was low in both groups. Handling of missing data was not described. Reporting Bias: (low) Study conducted per protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to participants who are Asian and slightly older than the average person with POAG. Intervention: Dose finding studies have demonstrated that the omidenepag dose is appropriate. Comparator: see above Outcomes: Changes in IOP is an appropriate primary outcome measure. Setting: Japan

		interfering with reliable Goldmann applanation tonometry - presence of any active external ocular disease, inflammation or infection of the eye or eyelids - history of other eye diseases - history of eye surgery - Pregnant people						

Key: * Noninferiority margin determined by the upper limit of the 2-sided 95% CI for the difference in the mean IOP of equal to or less than 1.5 mmHg at all 9 timepoints and equal to and less than 1.0 mmHg at a majority (5 or more) of the 9 timepoints; † Studies were identical in design and methods; however, study 01109IN had a 9-month open label treatment period.
Abbreviations: ARR = absolute risk reduction; CI = confidence interval; DB = double blind; IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OAG = open angle glaucoma; OHT = ocular hypertension; PP = per protocol; POAG = primary open-angle glaucoma; RCT = randomized controlled trial; SB = single blind

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
betaxolol HCl	BETAXOLOL HCL	DROPS	Y
brimonidine tartrate	ALPHAGAN P	DROPS	Y
brimonidine tartrate	BRIMONIDINE TARTRATE	DROPS	Y
brinzolamide	AZOPT	DROPS SUSP	Y
brinzolamide	BRINZOLAMIDE	DROPS SUSP	Y
carteolol HCl	CARTEOLOL HCL	DROPS	Y
dorzolamide HCl/timolol maleat	COSOPT	DROPS	Y
dorzolamide HCl/timolol maleat	DORZOLAMIDE-TIMOLOL	DROPS	Y
dorzolamide/timolol/PF	COSOPT PF	DROPERETTE	Y
dorzolamide/timolol/PF	DORZOLAMIDE-TIMOLOL	DROPERETTE	Y
latanoprost	LATANOPROST	DROPS	Y
latanoprost	XALATAN	DROPS	Y
latanoprost	XELPROS	DRPS EMULS	Y
pilocarpine HCl	ISOPTO CARPINE	DROPS	Y
pilocarpine HCl	PILOCARPINE HCL	DROPS	Y
timolol maleate	TIMOLOL MALEATE	DROPS	Y
timolol maleate	TIMOPTIC	DROPS	Y
travoprost	TRAVATAN Z	DROPS	Y
travoprost	TRAVOPROST	DROPS	Y
acetylcholine chloride	MIOCHOL-E	KIT	N
apraclonidine HCl	IOPIDINE	DROPERETTE	N
apraclonidine HCl	APRACLONIDINE HCL	DROPS	N
betaxolol HCl	BETOPTIC S	DROPS SUSP	N
bimatoprost	BIMATOPROST	DROPS	N
bimatoprost	LUMIGAN	DROPS	N
brimonidine tartrate	ALPHAGAN P	DROPS	N
brimonidine tartrate/timolol	BRIMONIDINE TARTRATE-TIMOLOL	DROPS	N
brimonidine tartrate/timolol	COMBIGAN	DROPS	N
brinzolamide/brimonidine tart	SIMBRINZA	DROPS SUSP	N
carbachol	MIOSTAT	VIAL	N
dorzolamide HCl	DORZOLAMIDE HCL	DROPS	N
dorzolamide HCl	TRUSOPT	DROPS	N
echothiophate iodide	PHOSPHOLINE IODIDE	DROPS	N
latanoprostene bunod	VYZULTA	DROPS	N
levobunolol HCl	LEVOBUNOLOL HCL	DROPS	N
netarsudil mesylat/latanoprost	ROCKLATAN	DROPS	N
netarsudil mesylate	RHOPRESSA	DROPS	N

pilocarpine HCl	VUITY	DROPS	N
tafluprost/PF	TAFLUPROST	DROPERETTE	N
tafluprost/PF	ZIOPTAN	DROPERETTE	N
timolol	BETIMOL	DROPS	N
timolol maleate	ISTALOL	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	SOL-GEL	N
timolol maleate	TIMOPTIC-XE	SOL-GEL	N
timolol maleate/PF	TIMOLOL MALEATE	DROPERETTE	N
timolol maleate/PF	TIMOPTIC OCUDOSE	DROPERETTE	N
bimatoprost	DURYSTA	IMPLANT	
tafluprost/PF	TAFLUPROST	DROPERETTE	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 13, 2023

Search Strategy:

#	Searches	Results
1	betaxolol.mp. or Betaxolol/	1022
2	brimonidine.mp. or Brimonidine Tartrate/	1967
3	brinzolamide.mp.	434
4	carteolol.mp. or Carteolol/	484
5	dorzolamide.mp.	1176
6	latanoprost.mp. or Latanoprost/	2168
7	pilocarpine.mp. or Pilocarpine/	9869
8	Timolol/ or timolol.mp.	5359
9	travoprost.mp. or Travoprost/	755
10	acetylcholine.mp. or Acetylcholine/	100439
11	apraclonidine.mp.	479
12	bimatoprost.mp. or Bimatoprost/	903
13	brimonidine.mp. or Brimonidine Tartrate/	1967
14	carbachol.mp. or Carbachol/	19263
15	dorzolamide.mp.	1176
16	echothiophate.mp.	461
17	latanoprostene.mp.	57
18	levobunolol.mp. or Levobunolol/	309
19	netarsudil.mp.	138
20	tafluprost.mp.	280
21	bimatoprost.mp. or Bimatoprost/	903
22	tafluprost.mp.	280

23	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	134560
24	limit 23 to (english language and humans and yr="2018 -Current")	5096
25	limit 24 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	140

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OMLONTI® safely and effectively. See full prescribing information for OMLONTI®.

OMLONTI® (omidenepag isopropyl ophthalmic solution) 0.002%, for topical ophthalmic use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------
Omlonti (omidenepag isopropyl ophthalmic solution) 0.002%, is a relatively selective prostaglandin E2 (EP2) receptor agonist, indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage is one drop in the affected eye(s) once daily in the evening. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.002% (0.02 mg/mL) of omidenepag isopropyl. (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Pigmentation (5.1)
- Eyelash changes (5.2)
- Ocular Inflammation (5.3)
- Macular Edema (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions with incidence ≥ 1% are conjunctival hyperemia (9%), photophobia (5%), vision blurred (4%), dry eye (3%), instillation site pain (3%), eye pain (2%), ocular hyperemia (2%), punctate keratitis (2%), headache (2%), eye irritation (1%), and visual impairment (1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Santen at 1-855-7-SANTEN (855-772-6836) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Appendix 4: Key Inclusion Criteria

Population	People with open angle glaucoma and ocular hypertension
Intervention	Topical medications approved for the treatment of glaucoma and ocular hypertension
Comparator	Placebo or active treatments
Outcomes	Intraocular pressure reduction, visual field changes and withdrawals due to adverse events
Setting	Outpatient

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Drug Use Evaluation: Pregabalin and Other Sedating Drugs

Plain Language Summary:

- Pregabalin can be prescribed for nerve pain. It also helps decrease anxiety for people with generalized anxiety disorder.
- In some people, pregabalin can make them feel sleepy, dizzy, and make them less alert. These side effects may be worse when pregabalin is combined with other medicines that have similar side effects. People who take pregabalin with opioids are at increased risk for these side effects, including death.
- This review of Oregon Health Plan pharmacy claims found that pregabalin is commonly prescribed with other medicines that can make these side effects worse. However, this review did not find that pregabalin was commonly prescribed with an opioid.
- The Oregon Health Plan fee-for-service program currently approves a pharmacy claim for pregabalin in a process called prior authorization. Because so few people in this review were prescribed pregabalin and opioids together, it may not be necessary to require prior authorization for pregabalin to address this safety concern.

Research Questions:

- In Oregon FFS Medicaid members with prescriptions for pregabalin, how many members had therapy that overlapped with opioids or other sedating drugs?

Conclusions:

- Prior authorization (PA) is currently required under the Oregon Health Plan (OHP) fee-for-service (FFS) program for all formulations of pregabalin.
- Concomitant use of other sedating drugs appeared to be common in members with paid claims for pregabalin. About 63% of members had at least one other sedating drug which overlapped with pregabalin by at least 5 days. About 22% of members with prescription claims for pregabalin had overlapping therapy with 2 or more other sedating drugs. However, our confidence in these findings is low because of the small overall population size.
- The most common type of sedating drug prescribed for OHP FFS members with pregabalin were muscle relaxants (27%; n=16). Seven members (12%) had concomitant opioid claims that overlapped with pregabalin claims.
- The Mental Health Clinical Advisory Group (MHCAG) discussed the role of pregabalin in the OHP FFS program and made the following recommendations to the Pharmacy and Therapeutics (P & T) Committee for consideration:[1]
    - Recommendation 1: Remove OHP FFS PA for pregabalin immediate-release (IR) capsule products.
        - Reason: The MHCAG recommends pregabalin IR as a first-line adjunct for patients with generalized anxiety disorder (GAD) on a SSRI/SNRI. Pregabalin IR has proven to be relatively safe, tolerable and effective for many conditions. The IR capsules have been generic for several years and is inexpensive.
    - Recommendation 2: Should the P & T Committee not agree with the MHCAG's first recommendation, the MHCAG asks that the P & T Committee consider this alternative: Add GAD to Table 1 of OHP FFS PA for pregabalin IR and do not require prior treatment or intolerance to gabapentin.
        - Reason: Gabapentin does not have evidence for treatment of GAD.

Recommendations:

- Make pregabalin immediate-release capsules preferred based on clinical evidence supporting use for GAD.
- Based on the lack of evidence for efficacy and safety between gabapentin and pregabalin, consider aligning coverage criteria for pregabalin and gabapentin by:
    - Removing PA for preferred pregabalin products OR
    - Adding PA for gabapentin to limit to evidence-supported indications
- Update prior authorization (PA) criteria as presented in **Appendix 2** to include GAD.
- Recommend removal of gabapentin step therapy for all conditions (including GAD). Instead, suggest trial of a preferred gabapentinoid product.
- If PA is maintained for pregabalin, automatically approve requests for preferred pregabalin in people with a recent history of an SSRI or SNRI, or when prescribed by a mental health specialist.

Background

Much of the increasing use of gabapentin and pregabalin can be attributed to the search for alternatives to opioids for the management of chronic pain. New guidance from the Centers for Disease Control (CDC) recommends use of non-opioid analgesics for chronic pain.[2] The guideline suggests considering gabapentin or pregabalin for certain chronic pain conditions, including diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.[2] However, the CDC also recognizes that gabapentinoids are associated with only small to moderate improvements and are not without adverse effects. Pregabalin also has evidence of benefit when prescribed in conjunction with a serotonin reuptake inhibitor (SRI), such as a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) for treatment of GAD. In February 2023, the MHCAG developed treatment algorithms for GAD and recommended pregabalin as first-line adjunct treatment for patients who do not benefit from multiple trials of SRI monotherapy.[1]

Adverse events associated with pregabalin use can include blurred vision, cognitive effects, sedation, weight gain, dizziness, peripheral edema, and risks when used in combination with opioids.[2] The Food and Drug Administration (FDA) issued a warning in 2019 of an increased risk of respiratory depression when used with opioids or other CNS depressants. Observational studies have shown an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk for overdose, with higher risks at increased gabapentinoid doses. This is consistent with recent data from the Department of Health and Human Services that gabapentin is increasingly detected in overdose deaths and highlights the risk of polysubstance use.[3] Pregabalin is a schedule V controlled substance. Pregabalin is currently not required to be reported to the Oregon Prescription Drug Monitoring Program (PDMP) though that policy may change with future legislation.

In the OHP FFS program, PA is required for pregabalin. The goal of the PA is to limit use to FDA-approved and OHP-funded indications. Gabapentin tablets and capsules are currently preferred products and are available without PA. Both drugs are categorized under Oregon law as physical health drugs so they are not carved out from coordinated care organization (CCO) coverage. Current criteria for pregabalin does not include any screening for concomitant opioids or other sedating drugs. However, clinical PA criteria for long-term use of any opioids under OHP FFS includes assessment for concomitant sedatives, including gabapentinoids.

In May 2018, the P & T Committee evaluated FFS utilization of gabapentin. That review identified no clear safety issues at the time for FFS members prescribed chronic gabapentin (>90 days).[4] Few members were on high doses of gabapentin (75% of members had ≤1800 mg daily). Over the course of the study from 2/1/15 to 6/30/17, co-prescribed gabapentin and opioids decreased from about 24.5% to 19.5%.[4]

The purpose of this review was to evaluate the concomitant prescription claims for pregabalin in combination with other sedating drugs.

Methods:
Members were identified for inclusion based on paid or denied FFS claims for pregabalin (HSN 026470). The evaluation window for pregabalin claims was from 7/1/21 to 6/30/22. The index event (IE) was defined as the first paid FFS claim in the evaluation window. For each FFS member, the baseline and follow-up periods were based on the IE. A short baseline and follow-up period of 35 days was chosen because most controlled substances and mental health medications have a maximum days' supply limit of 34 days. These short baseline and follow-up periods were intended to maximize the proportion of members included in the analysis, but may miss claims for some maintenance medications which can be filled for longer periods (e.g., 90 day fills).

- The baseline period was defined as the 35 days prior to the IE (exclusive of the IE).
- The follow up period was defined as the 35 days following the IE (inclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for pregabalin during the evaluation window.

Exclusion Criteria:

1. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline or follow-up periods;
2. Individuals with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline or follow-up periods. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM BMD MED	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug Oregon Health Plan with Limited Drug Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND CWM SMF SMB	Transplant package Citizenship Waived Emergency Medical Special Low-Income Medicare Beneficiary Only Special Low-Income Medicare Beneficiary Only

3. Non-continuous Medicaid eligibility during the baseline period; and
4. Non-continuous FFS eligibility during the follow-up period.

Outcomes:

This drug use evaluation (DUE) will evaluate the proportion of OHP FFS members with prescription claims for pregabalin and concomitant sedating drug(s) over a 12-month period. Sedating drugs were pre-defined based on PDL class. The following PDL classes were included: oral muscle relaxants, second-generation antipsychotics, first-generation antihistamines, benzodiazepines, opioids (long-acting or short-acting), and sedatives.

Paid FFS and CCO claims for concomitant drug therapy were evaluated during the baseline and follow-up periods (defined above). CCO claims were included to capture members who may transitioning out of a CCO. Members were categorized as having concomitant drug therapy if the claim for the sedating drug overlapped with the claim for pregabalin by 5 or more consecutive days. Days covered by a claim were calculated by adding the days' supply submitted on the claim to the date of service.

Results:

Over a 12-month period from 7/1/22 to 6/30/22, 138 members had paid FFS claims for pregabalin. After exclusion of people who likely had incomplete claims data, 60 members (43.5%) were included in this analysis. Most members with paid claims for pregabalin were adults (90%) and female (65%). About 37% of members identified as white and 55% identified as American Indian or Alaskan Native (**Table 2**). Overall, 63% of members had at least one other sedating drug which overlapped with pregabalin by at least 5 days **(Table 3)**. The most common sedating drugs identified were muscle relaxants (27%), second-generation antipsychotics (18%), first-generation antihistamines (17%), benzodiazepines (15%), and opioids (12%). About 22% of members with prescription claims for pregabalin had overlapping therapy with 2 or more other sedating agents. In people with a pregabalin claim, other sedating drugs were dispensed both before (55%) and after (45%) pregabalin.

Table 1. **Number of Included Members.**

Number of included OHP FFS Members	#	%
With paid FFS pregabalin claim from 7/1/2021 to 6/30/2022	**138**	
And after exclusion of limited benefit packages, Medicare, TPL	69	50.0%
And after continuous Medicaid enrollment requirement in the baseline period (35 days before the IE)	67	48.6%
And after continuous FFS enrollment requirement in the follow-up period (35 days after the IE)	**60**	43.5%

Table 2. Demographic Data of Members with Included FFS Pharmacy Claims.

	Member Count	
	60	%
Female	39	65.0%
Age – mean (range)	45	(6-66)
<18	3	5.0%
18-35	12	20.0%
36-64	42	70.0%
>=65	3	5.0%
Race		
White	22	36.7%
Unknown	4	6.7%
American Indian/Alaskan Native (HNA)	33	55.0%
Other	1	1.7%

Table 3. Members with Concomitant Claims with 5 or more Days Overlap with Pregabalin

	Member Count	
Pregabalin (denominator)	60	%
Concomitant sedating drug therapy (by PDL class)		
Muscle relaxant, oral	16	26.7%
Antipsychotics, second-generation	11	18.3%
Antihistamine, first-generation	10	16.7%
Benzodiazepines	9	15.0%
Opioid (long-acting or short-acting)	7	11.7%
Sedatives	1	1.7%
Number of unique drugs with >=5 days of overlap (by HSN)		
0	22	36.7%
1	25	41.7%
2	7	11.7%
3	4	6.7%
4	2	3.3%

Limitations and Discussion:

- This study evaluates a 12-month time period and data was based on prescription claims history which may not accurately reflect medication use.
- Concomitant drug therapy was defined as at least a 5-day overlap with a prescription claim for pregabalin and another sedating drug. However, such a short overlap could also include members who are switching therapy or using therapy acutely as needed rather than an indicator of ongoing concomitant treatment.
- The total number of members with FFS coverage for pregabalin is small. A significant proportion of members were excluded because they had potentially incomplete claims data due to other primary insurance or because they were not eligible for Medicaid for the required 35-day baseline or follow-up periods. The small number of members included in this analysis decreases our confidence in these results.
- This DUE did not compare pregabalin to gabapentin (which is available without PA). Removal of PA for pregabalin could potentially lead to increased co-prescribing with opioids, but the magnitude and clinical significance of this potential change is unknown. In a DUE evaluating FFS members prescribed chronic gabapentin from 2/1/15 to 6/30/17, a larger proportion of patients had co-prescribed gabapentin and opioids compared to the proportion of co-prescribed pregabalin and opioids identified in this DUE. However, this prior DUE also identified that co-prescribing of gabapentin and opioids was decreasing over time from 24% to 19% over this 2 year period, and it is not clear how these historical rates would compare to current prescribing patterns.
- This DUE only includes claims paid by OHP FFS, and any potential cash claims would not be included. Some patients may elect to pay cash rather than navigate the PA process. These members may not be identified with current PA criteria for sedatives and opioids that evaluate concomitant use of a sedating drug.

- The duration of concomitant drug therapy was not assessed in this analysis. Muscle relaxants, sedatives for insomnia, antihistamines, benzodiazepines, and opioids can be prescribed on an "as needed" basis. This analysis did not determine how many members had routine ongoing treatment with multiple agents compared to those who use these therapies less frequently. The clinical relevance of a brief overlap of pregabalin with as needed use of other sedating drugs is unknown.
- A short baseline and follow-up period (35 days each) was used in this study. Some drugs may be prescribed for longer periods (e.g., up to 90 days) if they are used as routine maintenance medications. Other drugs may be filled by members less frequently if they are used only as needed for acute symptom management. For both of these circumstances, the short baseline and follow-up period may result in incorrect categorization of concomitant medication use for members in this study.

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Drug Use Evaluation: Pregabalin – Indication Review

Plain Language Summary:

- Should the Oregon Health Plan change the current Medicaid policy for pregabalin to cover conditions that are not approved by the Food and Drug Administration (FDA)?
- Pregabalin can be prescribed for nerve pain. It also helps decrease anxiety for people with generalized anxiety disorder when it is prescribed with an antidepressant. Antidepressants that improve symptoms for people with generalized anxiety include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
- Studies have not shown that pregabalin improves pain in people with other pain-related conditions that are not FDA-approved.
- A review of Medicaid claims shows that providers commonly prescribe pregabalin for conditions that are not approved by the FDA. About 14% of people with claims for pregabalin have a diagnosis of generalized anxiety disorder.
- Currently, providers must tell Medicaid why they are prescribing pregabalin before Medicaid Open Card will pay for the prescription. This process is called prior authorization. This analysis of Medicaid data shows that prior authorization may decrease use of pregabalin for conditions where there is no benefit. But it may also delay care for people with generalized anxiety disorder or other conditions where there is benefit.
- The Mental Health Clinical Advisory Group recommended that pregabalin be available for people with generalized anxiety disorder when prescribed with an SSRI or SNRI. They recommended removal of prior authorization to reduce barriers to treatment for this population.
- We recommend that immediate-release pregabalin be available as a preferred option for people with Medicaid Open Card. The Pharmacy and Therapeutics Committee should consider removal of prior authorization for pregabalin or automatic approval of requests for preferred pregabalin when it is prescribed for generalized anxiety disorder.

Research Questions:

- What medical diagnoses are present in Oregon FFS Medicaid members prescribed pregabalin that are potential indications for therapy?
- What types of providers prescribe pregabalin in Oregon FFS Medicaid members?
- In people with a prescription for pregabalin, how many members were recently prescribed an SSRI or SNRI?

Conclusions:

- Overall, less than half of OHP members with FFS claims for pregabalin had an FDA-approved diagnosis (48%). The most common diagnoses identified in medical claims for members with claims for pregabalin included diabetic neuropathy or diabetes (29%), other neuropathies and nerve injury (14%), and fibromyalgia (17%).
- A diagnosis of generalized anxiety disorder (GAD) was present in the medical claims for 14% of members (n=26). Comorbid diagnoses were common in people with GAD, and 14 people (54%) with a diagnosis of GAD also had another FDA-approved diagnosis for pregabalin in their medical claims.

- General practitioners accounted for the majority of pregabalin claims and most commonly included family medicine physicians, family nurse practitioners, internal medicine physicians, and physician assistants.
- Less than half of members with a diagnosis of GAD were prescribed first-line therapy with an SSRI or SNRI (46%) in the previous month. Previous therapy with an SSRI or SNRI was even less common in patients without a GAD diagnosis.

Recommendations:

- Make pregabalin immediate-release capsules preferred based on clinical evidence supporting use for GAD.
- Based on the lack of evidence for efficacy and safety between gabapentin and pregabalin, consider aligning coverage criteria for pregabalin and gabapentin by:
    - Removing PA for preferred pregabalin products OR
    - Adding PA for gabapentin to limit to evidence-supported indications
- Update prior authorization (PA) criteria as presented in **Appendix 2** to include GAD.
- Recommend removal of gabapentin step therapy for all conditions (including GAD). Instead, suggest trial of a preferred gabapentinoid product.
- If PA is maintained for pregabalin, automatically approve requests for preferred pregabalin in people with a recent history of an SSRI or SNRI, or when prescribed by a mental health specialist.

Background

Use of gabapentinoids, including pregabalin, has been rising. Between 2012 and 2016, spending on pregabalin grew from $2 billion to nearly $4.5 billion. In a 2022 study, approximately 1 in 5 U.S. adults with chronic pain were receiving a gabapentinoid.[1,2] Much of the increased use has been attributed to the search for alternatives to opioids for the management of chronic pain. New guidance from the Centers for Disease Control calls for even greater use of non-opioid analgesics, including pregabalin.[3] The guidelines suggest considering gabapentin or pregabalin for certain chronic pain conditions, including diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.[3] The guidelines also indicate that they are associated with only small to moderate improvements and are not without adverse events such as blurred vision, cognitive effects, sedation, weight gain, dizziness, peripheral edema, and risks of respiratory depression and overdose when used in combination with opioids.[3]

Evidence directly comparing gabapentin to pregabalin are limited and are generally of poor quality with small sample sizes.[4] Among these small trials for chronic neuropathic pain, results are inconsistent with some trials showing small differences between gabapentin and pregabalin and the majority showing them to be equal.[4] Overall, there is insufficient evidence to discern the superiority of one agent over another.

For FDA approved indications, overall effect size of pregabalin in clinical studies is small.[4] Five studies were submitted to FDA for approval for diabetic peripheral neuropathy. Of those, the FDA rated three as being supportive, one as partly supportive and one as negative. Overall, the reduction in pain is modest, as measured on a 11-point Likert scale (ranging from 0-10). Additionally, the placebo response was at least 50% as large as the response to any pregabalin dose. For the treatment of fibromyalgia, there was a small difference seen in mean pain score with pregabalin 300 mg/day, 450 mg/day and 600 mg/day compared to placebo (difference of -0.71 to -1.0) with little additional benefit with the highest dose but more discontinuations due to adverse events.[4] Finally, cognitive adverse effects was a significant concern of FDA and most trials excluded patients from using other centrally acting medications during the study period, including opioids, which may underestimate adverse effects.

In contrast to the single pain indication for gabapentin, pregabalin is FDA approved for four pain related conditions, but it has been reported that most of the use is for off-label indications unsupported by evidence. There have been negative studies showing no significant benefit with pregabalin over placebo for

various chronic pain conditions, including sciatica pain, human immunodeficiency virus (HIV) neuropathy, chronic sickle cell pain, acute zoster pain, and back pain.[5-7]

FDA-approved indications for immediate-release pregabalin include neuropathic pain associated with diabetic peripheral neuropathy, postherpatic neuralgia, neuropathic pain associated with spinal cord injury, fibromyalgia, and treatment of partial-onset seizures. Extended release formulations are only FDA approved to treat neuropathic pain associated with diabetic peripheral neuropathy and postherpatic neuralgia. A variety of off-label conditions have been cited in the literature including:[9,10]

- acute and chronic pain conditions such as post-operative, dental, cancer, or sickle-cell pain
- neuropathic conditions such as trigeminal neuralgia, familial dysautonomia, essential tremor, and other polyneuropathies
- genitourinary conditions such as uremic pruritus, and ureteral stent-related symptoms
- psychiatric conditions such as GAD and social anxiety disorder
- sleep-related conditions such as restless leg syndrome
- vasomotor symptoms associated with menopause
- alcohol use disorder and alcohol withdrawal symptoms

In the OHP FFS program, PA is required for pregabalin. The goal of the PA is to limit use to FDA-approved and OHP-funded indications. Common conditions that are unfunded on the prioritized list include restless leg syndrome, fibromyalgia, and some polyneuropathies. Gabapentin tablets and capsules are currently preferred products and are available without PA. Both drugs are categorized under Oregon law as physical health drugs, so they are not carved out from coordinated care organization (CCO) coverage.

In February 2022, the Mental Health Clinical Advisory Group (MHCAG) developed treatment algorithms for generalized anxiety disorder (GAD). Pregabalin is recommended as first-line adjunct treatment for patient with GAD in conjunction with a SSRI/SNRI. The MHCAG discussed the role of pregabalin in the OHP FFS program and made the following recommendations to the Pharmacy and Therapeutics (P & T) Committee for consideration:[11]

- Recommendation 1: Remove OHP FFS PA for pregabalin immediate-release (IR) capsule products.
    - Reason: The MHCAG recommends pregabalin IR as a first-line adjunct for patients with generalized anxiety disorder (GAD) on a SSRI/SNRI. Pregabalin IR has proven to be relatively safe, tolerable and effective for many conditions. The IR capsules have been generic for several years and is inexpensive.
- Recommendation 2: Should the P & T Committee not agree with the MHCAG's first recommendation, the MHCAG asks that the P & T Committee consider this alternative: Add GAD to Table 1 of OHP FFS PA for pregabalin IR and do not require prior treatment or intolerance to gabapentin.
    - Reason: Gabapentin does not have evidence for treatment of GAD.

Methods:

OHP members were identified for inclusion based on paid or denied FFS claims for pregabalin (HSN 026470). The evaluation window for pregabalin claims was from 7/1/21 to 6/30/22. The index event (IE) was defined as the first paid or denied FFS claim in the evaluation window. For members with paid and denied claims on the same day, the IE was classified as paid. For each member, the baseline period was defined as the 6 months prior to the IE (exclusive of the IE).

Inclusion Criteria:

1. At least one FFS paid claim for pregabalin during the evaluation window OR

2. At least one FFS denied claim for pregabalin during the evaluation window associated with either error 3002 (NDC requires PA) or error 3000 (units exceed authorized units on pa master file) AND NOT associated with any of the error codes indicating non-coverage through FFS or billing errors (**Appendix 1**).

Exclusion Criteria:

1. Primary insurance coverage (i.e., third party liability [TPL]) at any time during the baseline period;
2. Individuals with Medicare Part D coverage or limited or no Medicaid drug benefit at any time during the baseline period. Claims data for these patients may be incomplete. Patients were identified based on the following benefit packages:

Category	Benefit Package	Description
Medicare Part D coverage	BMM	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug
	BMD	Oregon Health Plan with Limited Drug
	MED	Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND	Transplant package
	CWM	Citizenship Waived Emergency Medical
	SMF	Special Low-Income Medicare Beneficiary Only
	SMB	Special Low-Income Medicare Beneficiary Only

3. Non-continuous Medicaid eligibility during the baseline period

Outcomes evaluated in this analysis included:

- Number of members with an FDA-approved or pre-specified off-label diagnosis for pregabalin based on ICD-10 codes on medical claims during the baseline period or on the index date.
- Prescriber type defined based on taxonomy associated with the IE.
- Number of members with a GAD diagnosis and recent claims for an SSRI or SNRI.

Results:

A total of 438 people were identified who had paid or denied claims for pregabalin from 7/1/21 to 6/30/22. After application of exclusion criteria which removed any members who may have had incomplete claims data, 180 members (41.1%) were included in the analysis.

Demographics for members with paid or denied claims for pregabalin are listed in **Table 1**. Prior authorization is currently required for all forms of pregabalin, and the first claim for most people was denied (79%). Only a small percentage (15.6%) had recent claims for pregabalin in the 6 months prior to their first identified claim. People with prior therapy for pregabalin were more likely to have a paid claim in the evaluation window which would be expected for members with an approved PA already on file. The majority of people with claims for pregabalin were adults (>95%) who identified as female (64%). About 65% of people with claims for pregabalin were American Indians or Alaskan Natives, and about 28% of people identified as White.

Less than half of members (48%) had an FDA-approved diagnosis present in their recent medical claims (**Table 2**). In members without an FDA-approved diagnosis, about 22% of members had a diagnosis in medical claims indicative of an off-label indication referenced in compendia where evidence may favor efficacy. Chronic pain conditions and other types of anxiety (such as social anxiety disorder or panic disorder) without evidence for use of pregabalin were present in 31% of members. The most common diagnoses identified in medical claims for members with claims for pregabalin included diabetic neuropathy or diabetes (29%), other neuropathies and nerve injury (14%), and fibromyalgia (17%). A diagnosis of GAD was present for 14% of patients (n=26). Comorbid

diagnoses were common in people with GAD, and 14 people (54%) with a diagnosis of GAD also had another FDA-approved diagnosis in the 6 months prior to their first claim.

Because this analysis evaluated only the first claim in the reporting period, there are limited conclusions which can be drawn from the proportion of paid and denied claims. An initial denied claim for pregabalin likely correlates to a delay in care or a shift in costs to the patient, but the extent of this delay and cost was not quantified with this analysis. Compared to members with initial denied claims, initial paid claims were more common for members with FDA-approved and funded indications of diabetes (35% vs. 27%) and epilepsy (27% vs. 1%). Denied claims were more common for people with diagnosis of GAD (22 of 26 people; 84%) and other off-label conditions without evidence for use such as other chronic or nonspecific pain, migraine, and other anxiety disorders.

Common first-line treatments for GAD include SSRIs or SNRIs. Some SSRIs and SNRIs are also used for treatment of fibromyalgia, chronic pain, and neuropathies. In people with a diagnosis of GAD, less than half of members had a paid claim for a SSRI or SNRI in the prior 35 days (**Table 3**). Use of SSRIs and SNRIs was even less common in people without a GAD diagnosis.

General practitioners accounted for the majority of pregabalin claims (**Table 4**). The most common prescribers included family medicine physicians, family nurse practitioners, internal medicine physicians, and physician assistants. About 6% of people (n=10) had prescriptions written from a neurologist and about 2% (n=4) had prescriptions written by a provider specializing in pain.

Table 1. Demographic Data of Members with Included FFS Pharmacy Claims.

	Paid IE		Denied IE		Total	
	37	%	143	%	180	%
Female	24	64.9%	92	64.3%	116	64.4%
Age (years) – mean (range)	44	(15-66)	46	(6-67)	45	(6-67)
<18	2	5.4%	1	0.7%	3	1.7%
18-35	8	21.6%	34	23.8%	42	23.3%
36-64	25	67.6%	104	72.7%	129	71.7%
>=65	2	5.4%	4	2.8%	6	3.3%
Race						
White	14	37.8%	36	25.2%	50	27.8%
Unknown	4	10.8%	14	9.8%	18	10.0%
American Indian/Alaskan Native (HNA)	19	51.4%	88	61.5%	107	59.4%
Other	0	0.0%	5	3.5%	5	2.8%
Therapy Type						
New start (no pregabalin claims in the prior 6 months)	12	32.4%	140	97.9%	152	84.4%
Continuation (pregabalin claims in the prior 6 months) *	25	67.6%	3	2.1%	28	15.6%

* Because people are categorized by their first paid or denied claim, no members with IEs after 1/1/2022 can be classified as "continuation" by definition

Table 2. Diagnoses Present in Medical Claims for Members with FFS Claims for Pregabalin

	Paid IE		Denied IE		Total	
	37	%	143	%	180	%
FDA-approved indication	**24**	**64.9%**	**62**	**43.4%**	**86**	**47.8%**
Diabetic neuropathy (or diabetes dx)	13	35.1%	39	27.3%	52	28.9%
Fibromyalgia (unfunded)	7	18.9%	24	16.8%	31	17.2%
Epilepsy	10	27.0%	1	0.7%	11	6.1%
Postherpetic neuralgia (or herpes zoster)	0	0.0%	1	0.7%	1	0.6%
Spinal cord injury pain	0	0.0%	1	0.7%	1	0.6%
Off-label with some evidence for use*	**5**	**13.5%**	**34**	**23.8%**	**39**	**21.7%**
Other neuropathies and nerve injury	5	13.5%	20	14.0%	25	13.9%
Generalized anxiety disorder (GAD)	0	0.0%	12	8.4%	12	6.7%
Restless leg syndrome (unfunded)	0	0.0%	3	2.1%	3	1.7%
Post-operative pain (acute)	0	0.0%	2	1.4%	2	1.1%
Uremic pruritus	0	0.0%	1	0.7%	1	0.6%
Vasomotor menopause symptoms	0	0.0%	0	0.0%	0	0.0%
None of the Above	**8**	**21.6%**	**47**	**32.9%**	**55**	**30.6%**
Other common pain conditions						
Chronic pain	2	5.4%	17	11.9%	19	10.6%
Dorsalgia	1	2.7%	22	15.4%	23	12.8%
Spinal Disc Disorders	0	0.0%	9	6.3%	9	5.0%
Joint Pain	0	0.0%	7	4.9%	7	3.9%
Extremity Pain	1	2.7%	4	2.8%	5	2.8%
Osteoarthritis	0	0.0%	4	2.8%	4	2.2%
Migraine	0	0.0%	4	2.8%	4	2.2%
Cancer pain	0	0.0%	1	0.7%	1	0.6%
Other anxiety disorders	2	5.4%	14	9.8%	16	8.9%

*Off-label conditions with some evidence were identified based on compendia-support indicating evidence may favor efficacy.[9,10]
Note: Categories are mutually exclusive and members were excluded from subsequent categories if they had a diagnosis in a previous group.

Table 3. Previous therapy with an SSRI or SNRI in the 35 days before the IE

	Paid IE		Denied IE		Total	
	37	%	143	%	180	%
GAD Diagnosis	4		22		26	
SSRI/SNRI	3	75.00%	9	40.91%	12	46.15%
No SSRI/SNRI	1	25.00%	13	59.09%	14	53.85%
No GAD Diagnosis	33		121		154	
SSRI/SNRI	11	33.33%	24	19.83%	35	22.73%
No SSRI/SNRI	22	66.67%	97	80.17%	119	77.27%

Table 4. Most common prescribing providers for pregabalin

			Paid IE		Denied IE		Total	
			37	%	143	%	180	%
	Taxonomy	**Description**						
1	207Q00000X	PHYSICIAN-FAMILY MEDICINE	9	24.3%	38	26.6%	47	26.1%
2	363LF0000X	NURSE PRACTITIONER - FAMILY	10	27.0%	31	21.7%	41	22.8%
3	207R00000X	PHYSICIAN-INTERNAL MEDICINE	3	8.1%	14	9.8%	17	9.4%
4	363A00000X	PHYSICIAN ASSISTANT	1	2.7%	14	9.8%	15	8.3%
5	363AM0700X	PHYSICIAN ASSISTANT - MEDICAL	2	5.4%	10	7.0%	12	6.7%
6	2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY	3	8.1%	7	4.9%	10	5.6%
7	363L00000X	NURSE PRACTITIONER	2	5.4%	7	4.9%	9	5.0%
8	363LA2200X	NURSE PRACTITIONER - ADULT HEALTH	0	0.0%	3	2.1%	3	1.7%
9	2081P2900X	PHYSICIAN-PHYSICAL MEDICINE&REHAB-PAIN MEDICINE	0	0.0%	2	1.4%	2	1.1%
10	390200000X	STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	1	2.7%	1	0.7%	2	1.1%
11	363LW0102X	NURSE PRACTITIONER - WOMEN'S HEALTH	1	2.7%	1	0.7%	2	1.1%
12	213ES0103X	PODIATRIST - SURGERY	0	0.0%	2	1.4%	2	1.1%
13	208VP0014X	PHYSICIAN-PAIN MEDICINE-INTERVENTIONAL PAIN MEDICINE	0	0.0%	2	1.4%	2	1.1%
14	208100000X	PHYSICIAN-PHYSICAL MEDICINE&REHAB	0	0.0%	2	1.4%	2	1.1%

Limitations and Discussion:

- The goal of this analysis was to evaluate diagnoses for OHP FFS members prescribed pregabalin. Overall, less than half of people with claims for pregabalin had an FDA-approved diagnosis. A diagnosis of GAD was present in the medical claims for 14% of people (n=26) with claims for pregabalin. However, it is difficult to discern the exact indication for which pregabalin was prescribed based on claims data alone. Fourteen people (54%) with a

diagnosis of GAD also had another FDA-approved diagnosis in the 6 months prior to their first claim, and less than half of people with a diagnosis of GAD were prescribed first-line therapy with an SSRI or SNRI (46%).

- One limitation of this analysis is that we categorized people according to the first claim in the evaluation window and did not evaluate what proportion of members with an initial denial ultimately had a PA approved. Therefore, there are limited conclusions which can be drawn from the proportion of paid and denied claims. An initial denied claim for pregabalin likely correlates to a delay in care or a shift in costs to the patient, but the extent of this delay and cost was not quantified with this analysis. In the third quarter of 2022, about 18% of people had an initial paid claim for pregabalin, 15% of people with an initial denial had pregabalin subsequently covered by FFS within 90 days, 15% switched therapy to a different antiepileptic (such as gabapentin), and 51% did not have any paid claims for antiepileptics within the 90 days following the initial denial. The most common reasons for lack of follow-up claims included people who transitioned into a CCO who may have covered pregabalin (27%), people with other insurance on file which may have been billed (36%), and people without a PA submitted by the provider (27%).
- There are other inherent limitations with use of claims data including use of diagnostic data based on claims history which may be incomplete or not accurately reflect true patient diagnoses. Diagnostic data was evaluated only over a 6 month period, and diagnoses for members on stable maintenance therapy may be missed if they had infrequent provider visits.
- A significant proportion of people identified with paid FFS claims for pregabalin were ineligible for inclusion in this study because of exclusion criteria (59%). This study assumes that included members are still representative of the entire Medicaid population.
- A relatively short duration (35 days) was used to quantify recent treatment with an SSRI or SNRI. Members may have been categorized incorrectly if they had any missed doses or did not fill their prescription on time.

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Appendix 1: Drug Coding

Table A1. Error codes associated with denied claims that were excluded from the analysis

Error Code	Description
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
4999	THIS DRUG IS COVERED BY MEDICARE PART D
576	CLAIM HAS THIRD-PARTY PAYMENT
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
643	INVALID OTHER COVERAGE CODE
3343	Questionable TPL amount
628	Other Coverage Reject Code Required for OCC 3
505	THIRD PARTY PAYMENT AMOUNT MORE THAN CLAIM CHARGE
513	RECIPIENT NAME AND NUMBER DISAGREE
238	RECIPIENT NAME IS MISSING
2809	DOB IS INVALID
2808	DOB IS MISSING
219	QUANTITY DISPENSED IS MISSING
1000	BILLING PROVIDER ID NOT ON FILE
1040	PRESCRIBING PHYSICIAN NOT ENROLLED
1026	PRESCRIBING PHYSICIAN ID NOT ON FILE
205	PRESCRIBING PROVIDER ID MISSING

Table A2. Diagnoses codes associated with FDA-approved or off-label indications

Description	ICD-10 code(s)
FDA-approved indication	
Diabetic neuropathy (or diabetes dx)	E08x-E13x
Postherpetic neuralgia (or herpes zoster)	B02x
Fibromyalgia (unfunded)	M797
Epilepsy	G40x
Spinal cord injury pain	S14x, S24x, S34x

Off-label with some evidence for use	
Other neuropathies and nerve injury	see **Table A3**
Post-operative pain (acute)	G891x
Uremic pruritus	L29x, N185x-N186x, Z992
Restless leg syndrome (unfunded)	G2581
Generalized anxiety disorder (GAD)	F411x
Vasomotor menopause symptoms	N95x

None of the above	
Other common pain conditions	
- Chronic pain	G892x, G894
- Dorsalgia	M54x
- Spinal Disc Disorders	M50x-M53x
- Extremity Pain	M796x
- Joint Pain	M255x
- Cancer pain	G893
- Migraine	G43x
- Osteoarthritis	M15x-M19x
Other anxiety disorders	F410x, F413x-F419x

Table A3. Diagnosis codes associated with neuropathy or nerve injury

Description	ICD-10 code(s)
Tuberculous neuritis	A1783
Diphtheritic polyneuritis	A3683
Meningococcal retrobulbar neuritis	A3982
Late congenital syphilitic polyneuropathy	A5043
Late congenital syphilitic optic nerve atrophy	A5044
Late syphilitic neuropathy	A5215
Mumps polyneuropathy	B2684
Gammaherpesviral mononucleosis with polyneuropathy	B2701
Cytomegaloviral mononucleosis with polyneuropathy	B2711
Other infectious mononucleosis with polyneuropathy	B2781
Infectious mononucleosis, unspecified with polyneuropathy	B2791
Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere	G13x
Disorders of trigeminal nerve	G50x
Facial nerve disorders	G51x

Disorders of other cranial nerves	G52x
Cranial nerve disorders in diseases classified elsewhere	G53x
Nerve root and plexus disorders	G54x
Nerve root and plexus compressions in diseases classified elsewhere	G55x
Mononeuropathies of upper limb	G56x
Mononeuropathies of lower limb	G57x
Other mononeuropathies	G58X
Mononeuropathy in diseases classified elsewhere	G59x
Hereditary and idiopathic neuropathy	G60x
Inflammatory polyneuropathy	G61x
Other and unspecified polyneuropathies	G62x
Polyneuropathy in diseases classified elsewhere	G63x
Sequelae of inflammatory and toxic polyneuropathies	G65x
Idiopathic peripheral autonomic neuropathy	G90x
Rheumatoid polyneuropathy with rheumatoid arthritis	M055x
Systemic sclerosis with polyneuropathy	M3483
Neuralgia and neuritis, unspecified	M792
Injury of cranial nerve	S04x
Injury of nerves at shoulder and upper arm level	S44x
Injury of nerves at forearm level	S54x
Injury of nerves at wrist and hand level	S64x
Injury of nerves at hip and thigh level	S74x
Injury of nerves at lower leg level	S84x
Injury of nerves at ankle and foot level	S94x
Other specified myoneural disorders	G7089
Myoneural disorder, unspecified	G709

Table A4. Drug coding and definitions for SSRIs and SNRIs

HIC3	HSN	Generic
H2S	001655	fluoxetine HCl
H2S	006324	sertraline HCl
H2S	006338	fluvoxamine maleate
H2S	007344	paroxetine HCl
H2S	010321	citalopram hydrobromide
H2S	024022	escitalopram oxalate
H2S	025796	paroxetine mesylate

H7C	008847	venlafaxine HCl
H7C	026521	duloxetine HCl
H7C	035420	desvenlafaxine succinate
H7C	040202	desvenlafaxine
H7C	040632	levomilnacipran HCl
H7C	048091	venlafaxine besylate
H7Z	025800	olanzapine/fluoxetine HCl
H8P	037597	vilazodone HCl
H8T	040637	vortioxetine hydrobromide

Appendix 2: Proposed Prior Authorization Criteria

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release
- Auto-approve requests for preferred pregabalin products in the following circumstances:
  - Patients with a recent history of an SSRI or SNRI in the past 90 days.
  - Prescriptions written by a mental health specialist.

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 for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5
4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Is the request for adjunct pregabalin in addition to an SSRI or SNRI for treatment of generalized anxiety disorder?	**Yes:** Approve for 12 months	**No:** Go to #7
~~6.~~7. Is the request for a preferred product or ~~H~~has the patient tried and failed, or have contraindications or intolerance to, a preferred gabapentinoid ~~gabapentin~~ product ~~therapy~~ for 90 days ~~or have contradictions or intolerance to gabapentin~~?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of ~~gabapentin~~ a preferred gabapentinoid for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. Pregabalin formulations for specific indications based on available evidence

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	

Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Generalized Anxiety Disorder	X	
Non-funded		
Fibromyalgia	X	

P&T Review: *10/22 (SF); 10/21 (DM); 10/20; 1/19; 7/18; 3/18; 3/17*
Implementation: *10/1/18; 8/15/18; 4/1/17*

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Prior Authorization Criteria Update: Non-preferred Drugs in Select PDL Classes

Plain Language Summary:

- The Oregon Health Plan (OHP) maintains a list of the most evidence-based, cost-effective medicines to prescribe for fee-for-service (FFS) members. This list is called the Preferred Drug List (PDL). The PDL is organized into groups of related medicines called "classes."
- Medicines not on the PDL are called "non-preferred" drugs. Non-preferred medicines may be less effective, less safe, or more costly than PDL medicines. Providers must explain to the OHP why someone needs a non-preferred medicine before Medicaid will pay for it. This process is called prior authorization (PA).
- OHP will only pay for medicines that are safe and approved by the Food and Drug Administration (FDA) and/or supported by medical evidence or common medical guidelines.
- When OHP has paid for a non-preferred medicine and if the prescriber wishes to continue the medicine, we recommend allowing a longer approval time to decrease barriers to care, especially if the patient has already tried/failed many of the other PDL medicine choices.

Purpose of Update:

- Modify criteria for non-preferred drugs in select PDL classes to remove barriers from previously approved care and provide a pathway for safe, effective, and cost-effective therapy.

Recommendation:

- Update non-preferred drugs prior authorization (PA) criteria to allow approval durations of up to 12 months for patients with a previously approved PA **(Appendix 1)**.

Appendix 1. Proposed Prior Authorization Criteria

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- Ensure that non-preferred drugs are used appropriately for OHP-funded conditions in adults.
- Allow case-by-case review for members covered under the EPSDT program.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

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 a request for continuation of a drug and dose previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the dosing consistent with FDA-approved labeling?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this an OHP-funded diagnosis?	**Yes**: Go to #6	**No**: For current age ≥ 21: Pass to RPh. Deny; not funded by the OHP For current age <21 years: Go to #7.
6. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.

Approval Criteria		
7. 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 #8	**No:** Pass to RPh. Deny; medical necessity.
8. 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 and process appropriate PA.

Renewal Criteria		
1. Has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 available preferred products?	**Yes:** Approve for 12 months.	**No:** Go to #2
2. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No:** Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.

P&T / DUR Review: *4/23; 12/22; 4/22; 7/15, 9/10; 9/09; 5/09*
Implementation: *1/1/23; 5/1/22; 10/13/16; 8/25/15; 8/15; 1/1/11, 9/16/10*

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Policy Evaluation: Glucagon-Like Peptide-1 Receptor Agonist and Metformin in the Fee for Service Population

Plain Language Summary

- There are many different kinds, or classes of medicines, to treat type 2 diabetes mellitus to help lower sugar levels for people with type 2 diabetes mellitus.
- This report focuses on a class called glucagon-like-peptide-1 receptor agonists (GLP-1 RA). Some of the medicines in this class are also Food and Drug Administration (FDA) approved to treat heart disease and obesity.
- Providers must tell Medicaid why they are prescribing certain medications before Medicaid Open Card will pay for the prescription. This process is called prior authorization.
- In May 2019 the prior authorization (PA) for the GLP-1 RA class was changed. The preferred medicines were updated and the medicines classified as preferred received an automatic-PA approval when a person was already taking a different medicine called metformin. This update to the PA was done to make it simpler for patients already taking metformin to also get a GLP-1 RA.
- This report looks at GLP-1 RAs use between 2017-2022 to see if the automatic-PA changed use of GLP-1 RAs and metformin.
- Between 2017-2022, use of GLP-1 RA went up. The update to the PA could have impacted this increase by improving access to patients.
- Most patients continued taking metformin regularly after starting a GLP-1 RA.
- This class of medicine has FDA indications for heart disease and weight loss benefits, but there were few patients with heart disease and no change in use in those with type 2 diabetes mellitus and obesity.
- We do not recommend any new changes to the current PA policy for GLP-1 RAs.

Research Questions:

- How have the prescribing patterns and utilization of glucagon-like peptide-1 receptor agonists (GLP-1 RA) changed over time in response to clinical prior authorization changes implemented in May 2019?
- What percentage of patients continue to adhere to metformin after initiation of a GLP-1 RA?
- What are the common patient characteristics and comorbidities (e.g., obesity) associated with those prescribed GLP-1 RA?

Conclusions:

- There was a sustained increase in utilization of GLP-1 RA from 2017-2022, consistent with expanded use in clinical practice. The change to the prior authorization criteria to automatically approve preferred GLP-1 RA medications for patients with prior claims of metformin, may have improved access for patients.
- Of the patients prescribed metformin before initiating a GLP-1 RA, 84.2% vs 87.5% had continued use of metformin after starting second-line treatment, with a percent daily coverage of 83.6% vs. 85.8% between the two groups, which showcased high adherence to the medication.
- GLP-1 RAs have indications for use in cardiovascular disease and weight loss, but there were few patients [on GLP-1 RAs] with atherosclerotic cardiovascular disease (ASCVD) and no change in use was observed in those with concomitant type 2 diabetes mellitus (T2DM) and obesity.

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Recommendations:

- Maintain current prior authorization (PA) policy for GLP-1 RAs.

Background

In the United States (US), 37.3 million people, or 11.3% of the population, have diabetes. Diabetes mellitus can be classified as either type 1 (T1DM) or type 2 (T2DM). Type 1 DM is caused by destruction of the insulin producing beta cells of the pancreas and is classified as an autoimmune disease or insulin-dependent diabetes. In contrast, T2DM is highly influenced by genetic and environmental factors, where blood glucose levels become chronically high due to deficits in insulin function that can lead to insulin resistance.[6] Both forms can result in serious health complications, and T2DM is the seventh leading cause of death in the US.[1] There is no cure for DM but morbidity and mortality can be reduced with lifestyle interventions, medications, and regular monitoring both at home and by health care providers. The leading cause of morbidity and mortality for individuals with T2DM is ASCVD, defined as acute coronary syndrome, stable/unstable angina, coronary revascularization, transient ischemic attack, stroke, peripheral artery disease and myocardial infarction.[2]

Metformin is the preferred first-line oral blood glucose-lowering agent to manage T2DM. This medication has become the most prescribed blood glucose-lowering therapy worldwide due to its favorable benefit in regards to clinical efficacy in controlling T2DM and cost effectiveness.[5] Other oral medication classes used for T2DM include sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are also indicated for chronic heart failure as well as reduction in atherosclerotic cardiovascular disease risk and kidney disease with or without diabetes, dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas[2]. Insulins are also used for some T2DM patients if they fail to achieve desired glucose goals, or have contraindications with oral therapy. Regarding other options to control T2DM, the use of GLP-1 RAs have continued to increase over the past couple of years due to their ASCVD risk reduction benefit and weight loss[4]. The GLP-1 RAs are FDA-approved for use in patients with T2DM, and two GLP-1 RAs (Saxenda and Wegovy) are FDA-approved for weight loss without concomitant T2DM (**Table 2**). The 2022 American Diabetes Association (ADA) guidelines classified GLP-1 RA as an appropriate initial therapy with or without metformin for individuals with T2DM who have, or are at high risk for, ASCVD, heart failure or chronic kidney disease. A small risk reduction in all-cause mortality with exenatide ER and liraglutide have been found as well as a moderate reduction in risk for CV death/CV events with dulaglutide, liraglutide and injectable semaglutide. Since there is no universally accepted second-line medication, the choice should be based on the degree of glucose lowering necessary to help the patient reach their target HbA1c levels, their unique characteristics and the risks associated with the therapy.[2]

Metformin step therapy is required for Oregon Health Plan (OHP) fee-for-service (FFS) participants before a PA for additional T2DM medications will be approved. Prior authorization requirements and medication status on the Preferred Drug List (PDL) for medications to treat T2DM have changed over time (**Table 1**). For patients with OHP FFS, PA requirements changed in May 2019 to allow automatic approval for preferred GLP-1 RAs for patients currently on metformin (defined as a metformin claim in the previous 40 days). This auto-PA eliminates the need to send manual PA requests for preferred GLP-1 RAs (**Table 2**). Dulaglutide was added as a preferred agent and became eligible for the auto-PA in September 2020. Exenatide and liraglutide were preferred formulary options when the auto-PA was initially implemented, which was determined after evaluation of efficacy and cost.

The purpose of this drug use evaluation is to determine how the PA revisions (**Table 1**) affected utilization of both metformin and GLP-1 RAs among OHP FFS members. Additionally, effects on metformin adherence and prevalent patient comorbidities among this population will be evaluated.

Table 1: Updates to Glucagon Like Peptide-1 Receptor Agonist Prior Authorization Criteria

Implementation Date		
February 1, 2015	**May 1, 2019**	**September 1, 2020**
- Include at least one GLP-1 RA on the PDL as a preferred third-line option for T2DM after metformin and a sulfonylurea - **Preferred GLP-1 RA:** exenatide (BYETTA) - All GLP-1 RAs subject to clinical PA criteria	- Modified clinical PA criteria to allow use of basal insulin when in combination with a GLP-1 RA - Allow auto-PA for preferred GLP-1 RA in patients with claims for metformin in the previous 40 days - **Preferred GLP-1 RA:** liraglutide (VICTOZA and exenatide (BYETTA)]	- Step therapy was removed from the clinical PA criteria for all agents other than metformin - Auto-PA was still only allowed for preferred products. - **Preferred GLP-1 RA:** liraglutide (VICTOZA and exenatide (BYETTA), dulaglutide (TRULICITY)

Abbreviations: DPP-4 = Dipeptidyl Peptidase-4 Inhibitors; GLP-1 RA = Glucagon-like peptide-1 receptor agonist; PA = prior authorization; PDL = Preferred drug list; SGLT-2 = Sodium-glucose Cotransporter-2; T2DM = Type 2 diabetes mellitus

Table 2: GLP-1 RA FDA-Approved Uses and Preferred Status in OHP FFS.

Brand Name	Generic Name	Route	FDA Approved Uses	Preferred Drug List Status
BYDUREON	exenatide, extended-release	subcutaneous	Type 2 Diabetes mellitus	Nonpreferred
BYETTA	exenatide	subcutaneous	Type 2 Diabetes mellitus	Preferred
ADLYXIN	lixisenatide	subcutaneous	Type 2 Diabetes mellitus	Nonpreferred
VICTOZA	liraglutide*	subcutaneous	Type 2 Diabetes mellitus	Preferred
TRULICITY	dulaglutide	subcutaneous	Type 2 Diabetes mellitus	Preferred
OZEMPIC	semaglutide**	subcutaneous	Type 2 Diabetes mellitus	Nonpreferred
RYBELSUS	semaglutide	oral	Type 2 Diabetes mellitus	Nonpreferred
MOUNJARO	tirzepatide	subcutaneous	Type 2 Diabetes mellitus	Nonpreferred

- SAXENDA* and WEGOVY**brands are indicated for weight loss. Weight loss is not currently included in the Oregon Medicaid state plan

Methods:

All paid FFS pharmacy claims for any GLP-1 RA (**Table 2**) from May 2017 to July 2022 was assessed and reported as per-member-per-month (PMPM).

In order to assess utilization of both metformin and GLP-1 RA and evaluate implementation of the auto-PA in May 2019, pre- and post-policy change cohorts were identified of patients who were newly started on a GLP-1 RA. Patients with a new, paid pharmacy claim for any GLP-1 RA from May 1, 2018 through April 30, 2019 were defined as the control group (pre-policy change), and patients with a new claim from May 1, 2019 through April 30, 2020 were defined as the

study group (post-policy change). Patients were assumed to be treatment-experienced if they met the following criteria: 1) had prior claims for GLP-1 RA paid by OHP; 2) the pharmacy indicated that the first paid claim was a refill; or 3) the member did not have any paid medical claims during the two-timeline cohort. Patients with less than 6 months of continuous enrollment prior to the first paid GLP-1 RA claim in FFS Medicaid were excluded. Descriptive statistics and percentages were used to evaluate changes between the cohorts. Patients were categorized by demographics, common comorbidities using ICD-10 codes (**Appendix 1**), and concurrent insulin use (**Appendix 2**). Common comorbidities were collected from OHP members from the last 6 months of medical records before the first GLP-1 RA claim. Insulin utilization was evaluated based on pharmacy claims in the 3 months prior to the first paid GLP-1 RA claim.

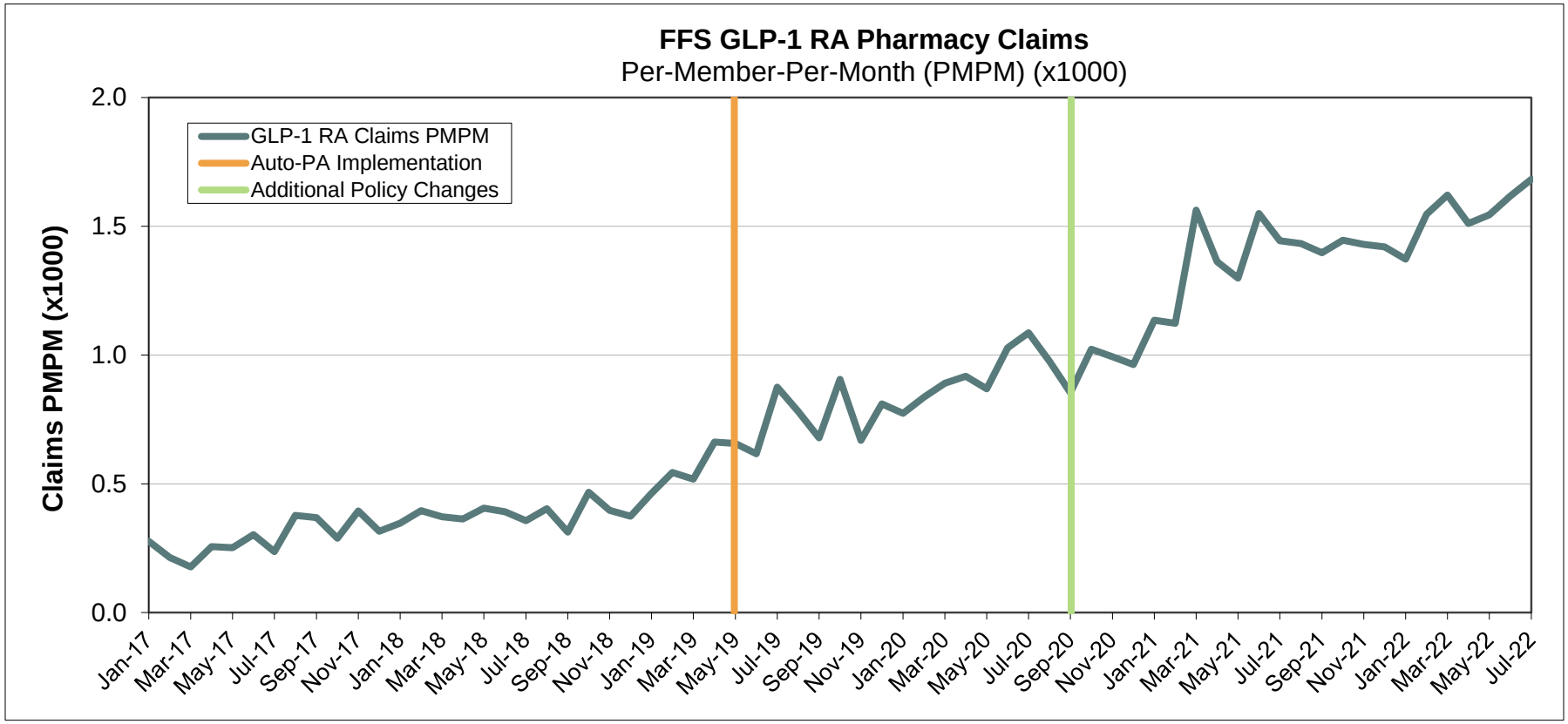
The percentage of patients who continued to adhere to metformin after GLP-1 RA initiation was compared in the pre and post cohorts. Metformin adherence was quantified by looking at actual daily coverage of the medication in the 3 months following the GLP-1 RA new start. Three months was chosen as a base to quantify metformin adherence due to the possibility that some prescriptions having been filled for a 90-day supply as well as to demonstrate adequate trial of the medication. For patients on metformin, the average percent daily coverage (PDC) of metformin was described. Patients with primary insurance or third-party liability (TPL) were excluded from the metformin adherence study objective.

Lastly, differences among PA types (fax, phone, auto-PA, or web/provider portal) before and after the PA change were compared. Patients with new paid pharmacy claims as well as renewed claims for a GLP-1 RA were included. This data included patients with TPL.

Results:

Figure 1 represents the utilization of GLP-1 RA use PMPM (PMPM x1000) from May 1, 2017 to July 30, 2022 for OHP FFS members. GLP-1 RA utilization increased after the implementation of the auto-PA was implemented in May 2019, showcased by the orange line. The green line demonstrates when dulaglutide was added as a preferred GLP-RA option. Among Oregon FFS Medicaid patients, GLP-1 RA utilization increased from 2017 to 2022 with 0.28 PMPM claims in January 2017 to 1.68 PMPM claims in July 2022.

Figure 1. Trend of GLP-1 RA Utilization PMPM from May 2017 to July 2022



Demographics of OHP FFS members in the control and study groups are presented in **Table 3**. There were 85 GLP-1 RA new starts in the control group from May 2018 to April 2019 and 129 in the study group from May 2019 to April 2020. Baseline characteristics appear similar between groups. (**Table 3**). Most patients were adults 35-64 years of age (89.7%), female (66.4%), and White (36%). The most prescribed agents in each group were dulaglutide and liraglutide, with a slight increase in liraglutide utilization in the study group compared to the control (55% vs. 39%). There was also a slight increase in patients with a history of ASCVD in the study group compared to control (12.4% vs. 4.7%) and lower frequencies of hypertension (50% vs. 60%) and obesity (39.5% vs. 43.5%) in the study group vs. control, respectively. Approximately half the patients in the control and study groups were on insulin in the 3 months prior to GLP-1 RA initiation (41.2% vs. 48.8%).

Table 3. Demographics.

Characteristic	Control Group: 5/1/18 – 4/30/19	Study Group: 5/1/19 – 4/30/20
Total New GLP-1 RA Claims	N=85	N=129
Average Age, years (%)	48 years	48 years
18-34	9 (10.6%)	12 (9.3%)
35-64	75 (88.2%)	117 (90.7%)
>65	1 (1.2%)	0 (0%)
Sex		
Male	32 (37.6%)	40 (31.0%)
Female	53 (62.4%)	89 (69.0%)
Race/Ethnicity		
Unknown	19 (22.4%)	40 (31.0%)
White	33 (38.8%)	44 (34.1%)
Hispanic	9 (10.6%)	8 (6.2%)
Other	10 (11.8%)	10 (7.8%)
GLP-1 RA Medication		
Dulaglutide	32 (37.6%)	35 (27.1%)
Exenatide	3 (3.5%)	6 (4.7%)
Exenatide microspheres	13 (15.3%)	10 (7.8%)
Liraglutide	33 (38.8%)	71 (55%)
Semaglutide	4 (4.7%)	7 (5.4%)
Diagnoses 6 Months Prior to New Start		
Any ASCVD History	4 (4.7%)	16 (12.4%)
Chronic Kidney Disease	7 (8.2%)	10 (7.8%)
Heart Failure	3 (3.5%)	6 (4.7%)
Hypertension	51 (60%)	64 (49.6%)
Obesity	37 (43.5%)	51 (39.5%)
Type 2 Diabetes	81 (95.3%)	114 (88.4%)
Insulin Claim 3 Months Prior to GLP-1 RA New Start		
Any insulin	35 (41.2%)	63 (48.8%)
Basal	31 (36.5%)	60 (46.5%)
Bolus	17 (20%)	22 (17.1%)
Basal/Bolus Combo products	0 (0%)	1 (0.8%)
Basal/GLP-1 RA Combo Products	0 (0%)	0 (0%)
Patients With TPL at Time of New GLP-1 RA New Start	29 (34.1%)	30 (23.3%)

In patients who had Medicaid as a primary payer, 67.9% (pre) vs. 64.6% (post) of patients had claims for metformin in the 3 months before initiating a GLP-1 RA at baseline (**Table 4**). Of the patients who had metformin at baseline, most continued metformin (84.2% vs 87.5%) after starting a GLP-1 RA. A small number of patients started metformin after initiation of a GLP-1 RA (5 vs 17%) who were not on it at baseline but 15.8% vs 12.5% discontinued metformin after starting a GLP-1 RA. The average percent-daily-coverage of metformin was similar in each group (83.6% vs. 85.8%).

Table 4: Metformin Utilization with New Start GLP-1 RA Use in OHP FFS Members (Excluding Patients with TPL Insurance)

	Control Group 5/1/18 – 4/30/19	**Study Group** 5/1/19 – 4/30/20
Total New GLP-1 RA Claims Without TPL	N=56	N=99
Metformin Use at Baseline in 3 months Before GLP-1 RA New Start	**38 (67.9%)**	**64 (64.6%)**
Continued Metformin After GLP-1 RA New Start	32 (84.2%)	56 (87.5%)
Discontinued Metformin after GLP-1 RA New Start	6 (15.8%)	8 (12.5%)
No Metformin Use at Baseline in 3 Months Before GLP-RA New Start	**18 (32.1%)**	**35 (35.4%)**
Started Metformin in 3 Months After GLP-1 RA	1 (5.6%)	6 (17.1%)
No Metformin Use After GLP-1 RA New Start	17 (94.4%)	29 (82.9%)
Average Percent Daily Coverage (PDC) of Metformin in Subsequent Three Months	83.6%	85.8%

Table 5 describes the differences between pre- and post-auto-PA implementation among types of PAs requested for a GLP-1 RA. In the year prior to implementation, there were a total of 222 PAs compared to 334 PAs one year after implementation. The proportion of fax and phone PAs decreased in the year after the change (post auto-PA) compared to the previous year (fax 49.7% vs. 64%; phone 24.9% vs. 34.2%), with 24% of the PAs processed as auto-PAs.

Table 5: PA Classification for GLP-1 Medications

	One Year Prior to Auto-PA Implementation 5/1/18 – 4/30/19	**One Year After Auto-PA Implementation** 5/1/19 – 4/30/20
Number of GLP-1 RA PAs	222	334
PA Type (%)		
Fax	142 (64%)	166 (49.7%)
Phone	76 (34.2%)	83 (24.9%)
Auto-PA	0 (0%)	80 (24%)
Web/Provider Portal	4 (1.8%)	5 (1.5%)

Discussion:
This DUE demonstrates trends in GLP-1 RA utilization following implementation of an auto-PA. As of May 2019, all patients with a pharmacy claim for metformin in the previous 40 days received auto-PA approval when a preferred GLP-1 RA was requested. **Figure 1** showcases the consistent increase in utilization of GLP-1 RAs from 2017-2022, with higher overall increase in claims after the auto-PA implementation. GLP-1 RA utilization increased from 2017 to 2022 with 0.28 PMPM claims in January 2017 to 1.68 PMPM claims in July 2022. Virtually, most of the increased utilization occurred with liraglutide, which is consistent with the PA change when it was made a preferred option with the auto-PA update in May 2019.

GLP-1 RA use in OHP FFS members has increased for several reasons, including increased prescriber familiarity with GLP-1 RAs, expanded indications as well as recommendations by guidelines for their use. The changes in clinical PA criteria and increasing the number of preferred products from 1 agent to 3 over time, may have also improved patient access by reducing barriers to prescribing. Data from **Table 5** show an overall increase in GLP-1 PAs but decreased use of both fax and phone PA types. The decrease in manual PAs after implementation of the auto-PA could have reduced barriers to prescribing.

Adherence to metformin was evaluated in this DUE because metformin continues to be recommended as a first-line treatment for T2DM (**Table 4**). Results regarding metformin use at baseline was lower than expected (67.9% (pre) vs. 64.6% (post), since use of metformin at baseline is a requirement for auto-PA approval. Patients who continued metformin after starting GLP-1 RA was appropriate, given the requirements needed. The moderate percentage of patients who discontinued metformin after initiating a GLP-1 RA is likely due to either an intolerance, contraindication to metformin, not following guideline directed therapy or possibly already taking an alternative agent. The high percentages of manual PAs that were submitted by fax or phone corresponds to the significant proportion of patients who were prescribed a non-preferred GLP-1 RA or did not have a recent metformin claim. Most patients who continued metformin, remained adherent in both groups, with PDC of >80%.

Despite indications for use in cardiovascular disease and weight loss, there were relatively few patients with a diagnosis of ASCVD or obesity in medical claims and no change in use in those with these concomitant diagnoses among the control and study groups.

DUE Limitations:
Retrospective claims data have inherent limitations. Causality cannot be determined and results should be interpreted with caution. Medication claims from pharmacies were used as a surrogate for metformin adherence. Using claims data also may have impacted the data collected regarding comorbidities and baseline characteristic since analysis relies on ICD-10 codes. When utilizing claims history data, the assumption is made that the medications of interest are being prescribed for the diagnosis of interest and not for any off-label use. Delays in submission and processing of medical claims may result in incomplete information.

The OHP includes a significant proportion of patients who are only transiently enrolled in FFS. Often patients are quickly enrolled into a CCO upon eligibility for OHP and remain in FFS for only a few months. To accurately capture data from this population in the analysis, patients with less than 6 months of continuous enrollment in OHP FFS were excluded. This limitation did lead to several assumptions when identifying patients who may be treatment-naïve, as only patients newly started on a GLP-1 RA were included in the study. Patients were assumed to be treatment-experienced if they met the following criteria: 1) had prior claims for GLP-1 RA paid by OHP; 2) the pharmacy indicated that the first paid claim was a refill; or 3) the member did not have any paid medical claims during the two timeline cohorts. Patients with a remote history of medication use would not be captured. There are also limitations when using PDC calculations as patients do not necessarily consume all the drugs filled. Additionally, exclusion of patients with incomplete or atypical administrative claims data (e.g.

percentage eligibility, third-party insurance) limits sample size and may not represent utilization across the OHP FFS population or the Oregon Medicaid population.

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6. Centers for Disease Control and Prevention. What is Diabetes?. Updated July 7 2022. Accessed August 10, 2022. Available from: https://www.cdc.gov/diabetes/basics/diabetes.

Appendix 1: ICD-10 Codes Used for Patient Demographics

Any ASCVD History: I25x	CKD: N18x
Acute Coronary Syndrome: I24x	Obesity: E66x
Stable/Unstable Angina: I20x	Metabolic Syndrome: E88x (counted as Obesity)
Stroke: G45x	Heart failure: I50x
Peripheral Artery Disease: I73x	Type 2 Diabetes: E11x
Myocardial infarction: I21x	Hypertension: I10x

Appendix 2: List of Insulin Products

Bolus Insulin		
Generic	Brand	Route/Form
Insulin regular, human	HUMULIN R U-500	Subcutaneous/vial
Insulin regular, human	AFREZZA	Inhalation/cartridge
Insulin regular, human	HUMULIN U-500 KWIKPEN	Subcutaneous/pen
Insulin lispro	ADMELOG	Subcutaneous/vial
Insulin lispro	HUMALOG	Subcutaneous/vial
Insulin lispro	INSULIN LISPRO	Subcutaneous/vial
Insulin lispro	HUMALOG	Subcutaneous/cartridge
Insulin lispro	ADMELOG SOLOSTAR	Subcutaneous/pen
Insulin lispro	HUMALOG KIWKPEN U-100	Subcutaneous/pen
Insulin lispro	INSULIN LISPRO KWIKPEN U-100	Subcutaneous/pen
Insulin lispro	HUMALOG KWIKPEN U-200	Subcutaneous/pen
Insulin lispro	HUMALOG JUNIOR KWIKPEN	Subcutaneous/Pen HF
Insulin lispro	INSULIN LISPRO JUNIOR KWIKPEN	Subcutaneous/Pen HF
Insulin aspart	INSULIN ASPART PENFILL	Subcutaneous/cartridge
Insulin aspart	NOVOLOG PENFILL	Subcutaneous/cartridge

Basal Insulin		
Generic	Brand	Route/Form
Insulin glargine, hum.rec.analog	Insulin glargine	Subcutaneous/vial
Insulin glargine, hum.rec.analog	LANTUS	Subcutaneous/vial
Insulin glargine, hum.rec.analog	SEMGLEE	Subcutaneous/vial
Insulin glargine, hum.rec.analog	BASAGLAR KWIKPEN U-100	Subcutaneous/pen
Insulin glargine, hum.rec.analog	INSULIN GLARGINE SOLOSTAR	Subcutaneous/pen
Insulin glargine, hum.rec.analog	LANTUS SOLOSTAR	Subcutaneous/pen
Insulin glargine, hum.rec.analog	SEMGLEE PEN	Subcutaneous/pen
Insulin glargine, hum.rec.analog	TOUJEO SOLOSTAR	Subcutaneous/pen
Insulin glargine, hum.rec.analog	TOUJEO MAX SOLOSTAR	Subcutaneous/pen
Insulin detemir	LEVEMIR FLEXTOUCH	Subcutaneous/pen
Insulin detemir	LEVEMIR	Subcutaneous/vial
Insulin glulisine	APIDRA	Subcutaneous/vial
Insulin glulisine	APIDRA SOLOSTAR	Subcutaneous/pen
Insulin degludec	TRESIBA FLEXTOUCH U-100	Subcutaneous/pen
Insulin degludec	TRESIBA FLEXTOUCH U-200	Subcutaneous/pen
Insulin degludec	TRESIBA	Subcutaneous/vial

Insulin aspart	INSULIN ASPART	Subcutaneous/vial
Insulin aspart	NOVOLOG	Subcutaneous/vial
Insulin aspart	INSULIN ASPART FLEXPLEN	Subcutaneous/pen
Insulin aspart	NOVOLOG FLEXPEN	Subcutaneous/pen
Insulin aspart (niacinamide)	FIASP PENFILL	Subcutaneous/cartridge
Insulin aspart (niacinamide)	FIASP FLEXTOUCH	Subcutaneous/pen
Insulin aspart (niacinamide)	FIASP	Subcutaneous/vial
Insulin aspart	LYUMJEV	Subcutaneous/vial
Insulin aspart	LYUMJEV KWIKPEN U-100	Subcutaneous/pen
Insulin aspart	LYUMJEV KWIKPEN U-200	Subcutaneous/pen
Insulin regular, human	HUMULIN R	Subcutaneous/vial
Insulin/ regular, human	NOVOLIN R	Subcutaneous/vial
Insulin regular/ human	NOVOLIN R FLEXPEN	Subcutaneous/pen

Combo Basal/bolus		
Generic	Brand	Route/Form
Insulin NPH hum/reg insulin hm	HUMULIN 70-30	Subcutaneous/vial
Insulin NPH hum/reg insulin hm	NOVOLIN 70-30	Subcutaneous/vial
Insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	Subcutaneous/pen
Insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	Subcutaneous/pen
Insulin aspart prot/insulin asp	INSULIN ASPART PROT MIX 70-30	Subcutaneous/pen
Insulin aspart prot/insulin asp	NOVOLOG MIX 70-30 FLEXPEN	Subcutaneous/pen
Insulin aspart prot/insulin asp	INSULIN ASPART PROT MIX 70-30	Subcutaneous/vial

Insulin glargine-yfgn	INSULIN GLARGINE-YFGN	Subcutaneous/vial
Insulin glargine-yfgn	SEMGLEE (YFGN)	Subcutaneous/vials
Insulin glargine-yfgn	INSULIN GLARGINE-YFGN	Subcutaneous/pen
Insulin glargine-yfgn	SEMGLEE (YFGN) PEN	Subcutaneous/pen
Insulin NPH human isophane	HUMULIN N	Subcutaneous/vial
Insulin NPH human isophane	NOVOLIN N	Subcutaneous/vial
Insulin NPH human isophane	HUMULIN N KWIKPEN	Subcutaneous/pen
Insulin NPH human isophane	NOVOLIN N FLEXPEN	Subcutaneous/pen
Combo Basal/GLP-1 Subcutaneous pen		
Insulin degludec/liraglutide	XULTOPHY 100-3.6	Subcutaneous/pen
Insulin glargine/lixisenatide	SOLIQUA 100-33	Subcutaneous/pen

Insulin aspart prot/insulin asp	NOVOLOG MIX 70-30	Subcutaneous/vial
Insulin lispro protamine/lispro	HUMALOG MIX 75-25 KWIKPEN	Subcutaneous/pen
Insulin lispro protamine/lispro	INSULIN LISPRO PROTAMINE MIX	Subcutaneous/pen
Insulin lispro protamine/lispro	HUMALOG MIX 50-50 KWIKPEN	Subcutaneous/pen
Insulin lispro protamine/lispro	HUMALOG MIX 75-25	Subcutaneous/vial
Insulin lispro protamine/lispro	HUMALOG MIX 50-50	Subcutaneous/vial

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

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. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *10/22 (KS), 8/20 (KS), 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: teplizumab-mzwv, injection

Date of Review: April 2023
Generic Name: teplizumab-mzwv

End Date of Literature Search: 01/04/23
Brand Name (Manufacturer): Tzield™ (Provention Bio, Inc)

Dossier Received: yes

Plain Language Summary:

- This review evaluates a new medicine called teplizumab that the U.S. Food and Drug Administration (FDA) approved to delay onset of type 1 diabetes. The FDA approved teplizumab only for people that have a high chance of developing type 1 diabetes.
- Type 1 diabetes is a disease where the body's immune system mistakes its own healthy cells as foreign and attacks them. This destroys pancreas cells that make insulin and causes high blood sugar.
- In people who were at risk of getting type 1 diabetes, teplizumab delayed the occurrence of diabetes by approximately two years compared to placebo or no treatment.
- A study showed that teplizumab did not improve blood sugars for people who already have diabetes.
- Teplizumab side effects were rash, blood problems, headache and liver problems.
- We recommend that only diabetes specialists, called endocrinologists, prescribe teplizumab. We also recommend teplizumab be prescribed only to people who are at high risk of type 1 diabetes.

Research Questions:

1. What is the evidence for efficacy for teplizumab in delaying the progression of type 1 diabetes (T1D) in people that are at high risk of developing the disease?
2. What is the harms evidence associated with the use of teplizumab?
3. Are there specific subpopulations that would be more likely to benefit from the use of teplizumab?

Conclusions:

- The efficacy and safety of teplizumab was evaluated in two, phase 2, placebo-controlled trials and one phase 3 trial.[1–3]
- There is moderate quality of evidence that teplizumab delays the progression to T1D in people with stage 2 T1D at high risk of developing T1D (e.g., relative with diabetes, immunogenic markers and abnormal glucose tolerance) for approximately two years.[1]
- One phase 2 trial demonstrated preservation of c-peptide levels, which are indicative of endogenous insulin production, in those receiving teplizumab after 2 years of treatment compared to no treatment, based on low quality of evidence.[2]
- There is low quality evidence from a single phase 3 trial that teplizumab does not reduce insulin needs in people recently diagnosed with T1D.[3]

Author: Kathy Sentena, PharmD

- The most common adverse reactions associated with the use of teplizumab are rash, lymphopenia, leukopenia, headache and cytokine release syndrome (CRS).[4]
- There is insufficient long-term evidence for the use of teplizumab. Results are most applicable to those people that are White and under the age of 18 years of age who are at high risk of developing diabetes.

Recommendations:
- Implement prior authorization criteria to limit use to people with stage 2 T1D and high risk of progression to stage 3 T1D (**Appendix 2**).

Background:
Diabetes is characterized by a hemoglobin A1c (HbA1c)of 6.5% or higher and associated with symptoms such as polydipsia, polyuria, weight loss, fatigue, and diabetic ketoacidosis (DKA).[5] People with diabetes have an increased risk of morbidity and mortality, and diabetes is the seventh leading cause of death in the United States (US).[6] There are two types of diabetes; T1D and type 2 diabetes. Type 1 diabetes is autoimmune mediated beta-cell destruction resulting in loss of insulin production while type 2 diabetes (T2D) is a non-autoimmune loss of beta-cell insulin secretion, often coinciding with insulin resistance and metabolic syndrome.[5] Type 2 diabetes more commonly occurs in adulthood and T1D often presents in childhood or adolescents. People with T1D often present with polydipsia, polyuria, weight loss and lower body mass index (BMI). Up to half of those with T1D are diagnosed after an episode of diabetic ketoacidosis (DKA).[5] People with T2D are often above their optimal BMI, are diagnosed at an older age and don't often present with DKA.

Type 1 diabetes accounts for approximately 10% of the diabetes diagnoses, with an estimated occurrence of 64,000 new cases annually in the US.[7] In some people with genetic predisposition to T1D, progression through stages of asymptomatic loss of insulin production occurs before overt hyperglycemia. Stages are defined based on different clinical and laboratory parameters (**Table 1**).[5] Development of autoantibodies occurs in Stage 1. Stage 2 is characterized by impaired metabolic response to glucose but normal levels of glycosylated hemoglobin; supplemental insulin is not required. In stage 3 T1D, people develop hyperglycemia with clinical symptoms leading to the need for life-long exogenous insulin.[8] People with characteristics of stage 2 disease, immunologic markers of T1D and abnormal glucose tolerance, are at high risk for progression to stage 3 and development of hyperglycemia symptoms over time. Development of hyperglycemia requiring insulin for management usually occurs within 6 years of development of autoantibodies. The FDA states that the conversion rate to stage 3 T1D to be 25% at 6 months, 60% at 2 years and 75% at 4 years in those individuals with dysglycemia and stage 2 T1D.[8] The lifetime risk for developing T1D is near 100% in high-risk individuals.[8] Caucasians have a higher prevalence of T1D with children, teens and young adults most commonly diagnosed. The most common ages of diagnosis is between 4 and 7 years of age. Family history is the most common risk factor.

Table 1. Type 1 Diabetes Staging[5]

	Stage 1	Stage 2	Stage 3
Characteristics	▪ Autoimmunity ▪ Normoglycemia ▪ Presymptomatic	▪ Autoimmunity ▪ Dysglycemia ▪ Presymptomatic	▪ Automimmunity ▪ Overt hyperglycemia ▪ Symptomatic
Diagnostic Criteria	▪ Multiple islet cell autoantibodies ▪ No IGT or IFG	▪ Islet cell autoantibodies (usually multiple) ▪ Dysglycemia: IFG and/or IGT ▪ FPG 100-125 mg/dL	▪ Autoantibodies may become absent ▪ Diabetes by standard criteria

		▪ 2-h PG 140-199 mg/dL ▪ HbA1c 5.7-6.4% or ≥10% increase in HbA1c	
Abbreviations: FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; 2-h PG = 2 hour plasma glucose			

Individuals that have the persistent presence of two or more islet autoantibodies are almost 100% likely to develop diabetes.[5] Determinants of progression include; age of first detection of autoantibody, number of autoantibodies, autoantibody specificity and autoantibody titers.[5] Several autoantibodies have been linked to the development of T1D. Exogenous insulin administration causes all individuals to develop insulin autoantibodies and should not be used to determine the presence of immune mediated diabetes. Glutamic acid decarboxylase (GAD) antibodies have been identified in approximately 70% of those with T1D.[9] Insulinoma-associated protein 2 (IA-2) is also commonly found in individuals with T1D and usually appears later than GAD or other autoantibodies to insulin. Zinc transporter (ZnT8) has been identified as a autoantigen in 60-80% of those with T1D, which appears later and is lost soon after the onset of T1D.[9] Islet cell antibodies (ICA) are present with insulin producing pancreatic beta cells are injured and are used to estimate the risk of T1D. Microinsulin autoantibodies (mIAA) are least commonly associated with other antibodies and rarely is indicative of the development of diabetes if it is the only antibody present.[10]

There are several immunologic treatment options in development to prevent the progression to T1D by preserving beta-cell function.[1] Chronic immunosuppressive therapies, such as cyclosporin, have been studied as an option for delaying the loss of insulin secretion. Fc receptor non-binding anti-CD3 monoclonal antibodies, like teplizumab and otelixizumab (in development), target CD8+ lymphocytes that contribute to the destruction of beta-cells and have demonstrated the most promise.[1]

There is insufficient data on the most optimal outcome to measure the effectiveness of immunotherapy in people with T1D. The measurement of C-peptide is used in some studies to predict insulin levels and the progression to T1D.[11] C-peptide levels are an indication of endogenous insulin production. C-peptide is not metabolized by the liver, and therefore, is a better determinant of insulin production than glucose levels. Low levels of C-peptide are indicative of no or low insulin production by the pancreas and need for exogenous insulin. Important short-term outcomes of progression to T1D include risk of hyperglycemia and DKA and longer term outcomes are retinopathy, kidney disease, and cardiovascular disease.[12] Studies have shown that those who are diagnosed with T1D at an older age have higher C-peptide levels and lower risk of morbidity associated with clinical T1D.[11, 13]

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.

Clinical Efficacy:

Teplizumab was approved by the FDA in November of 2022.[4] Teplizumab is a CD-3 directed antibody indicated for use in adults and pediatric patients 8 years of age and older with Stage 2 T1D to delay the onset of Stage 3 T1D. Teplizumab should be used in people that have a confirmed diagnosis of Stage 2 T1D by documentation of at least two positive pancreatic islet autoantibodies (e.g., GAD autoantibodies, IAA, IA-2, ZnT8 and ICA) in those who have dysglycemia without overt hyperglycemia when using an oral glucose tolerance test (OGTT) or alternative method if OGTT is not available.[4] Teplizumab should not be used for T2D or gestational diabetes and patient clinical history should be reviewed prior to initiation to ensure the patient has not already developed clinical symptoms of diabetes indicative of stage 3 diabetes. Teplizumab is given as a one-time treatment course of an intravenous (IV) infusion over at least 30 minutes, once daily for 14 days. A complete blood count and liver enzyme tests should be performed prior to starting teplizumab. Teplizumab has been associated with

cytokine release syndrome (CRS), and premedication before each teplizumab infusion, for the first five doses, is recommended. Pre-medications include oral nonsteroidal anti-inflammatory (NSAIDs) or acetaminophen, an antihistamine and and/or an antiemetic.

Teplizumab was evaluated in one good quality phase 2 trial, one poor quality phase 2 trial (AbATE) and one fair quality phase 3 trial (PROTÉGÉ) (**Table 5**).[1–3] Only one of these trials provided evidence for the approved indication of delaying the onset of Stage 3 T1D in those with stage 2 T1D.[1] Participants in this phase 2 trial were identified through the TrialNet Natural History Study. This study offers risk screening for relatives of people with T1D as well as clinical studies that test ways to slow down and prevent disease progression. Eligible participants had to be at high risk of developing diabetes, which was defined as people who have relatives with T1D and confirmed presence of autoantibodies (**Table 2**). Participants were also required to have a degree of dysglycemia on an OGTT (defined as a fasting glucose level of 110 to 125 mg per deciliter [6.1 to 6.9 mmol per liter], a 2-hour postprandial plasma glucose level of at least 140 mg per deciliter [7.8 mmol per liter] and less than 200 mg per deciliter [11.1 mmol per liter], or a postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per deciliter on two occasions, within 52 days before enrollment).[1] The median age of study participant was 13.5 years, median HbA1c 5.2%, and 55% of participants were male.[1] Seventy-six participants were randomized to placebo or teplizumab given as one course of treatment over 14 days.[1] Dosing of teplizumab was the following in the phase 2 trials: 51 mcg/m^2 on day zero, 103 mcg/m^2 mcg on day one, 207 mcg/m^2 mcg area on day two, 413 mcg/m^2 on day three, 826 mcg/m^2 area on days four through 13. This regimen is comprised of slightly lower doses throughout taper and final dose compared to teplizumab labeling which recommends titration up to the highest dose of 1,030 mcg/m^2 for days 5 through 14.[1] Pre-medications were given to both the treatment and placebo group.

Participants in the Herold trial were followed for 745 days.[1] The median time to progression to T1D was longer in people treated with teplizumab compared to placebo, 48.4 months versus 24.4 months (hazard ratio [HR] 0.41; 95% CI, 0.22 to 0.78; p-value = 0.006).[1] The percentage of people that progressed to T1D was lower in people randomized to teplizumab compared to placebo, 43% versus 72%.[1] The progression to diabetes was highest in the first year after treatment compared to the second or third year following treatment. Diagnosis of T1D occurred in 7% of people taking teplizumab compared to 44% in the placebo group in the first year.[1] The FDA determined that the delay in the development of T1D by two years is clinically meaningful due to the benefits in quality of life, and a reduction in risk of complications.[8] Those diagnosed at an earlier age are more likely to develop diabetic ketoacidosis and DKA.

Table 2. Autoantibodies Present at Baseline in Participants in the Teplizumab Studies

Autoantibodies	Teplizumab	Placebo
Phase 2 Study[1]		
GAD65	40 (91%)	28 (88%)
Micro insulin (mIAA)	20 (45%)	11 (34%)
IA-2	27 (61%)	24 (75%)
ICA	29 (66%)	28 (88%)
ZnT8	32 (73%)	24 (75%)
Phase 2 Study (AbATE)[14]		
GAD-65	40 (76.5%)	24 (95.7%)
IA-2	51 (98.0%)	24 (95.7%)
Micro insulin (mIAA)	37 (70.6%)	18 (73.9%)
ZnT8	45 (86.3%)	16 (65.2%)
Phase 3 Study (PROTÉGÉ)[3]		

GAD-65	375 (89%)	89 (91%)
Human insulin	370 (88%)	88 (90%)
Islet cell 512	231 (56%)	53 (54%)
Abbreviations: GAD65 = glutamic acid decarboxylase 65; IA-2 = insulinoma-associated antigen 2 antibody; ICA = islet cell autoantibody; ZnT8 = zinc transporter 8		

In the second phase 2 trial (AbATE), participants were newly diagnosed with T1D (stage 3) and had positive autoantibodies.[2] The mean age of participants was 12 years and 59% were White.[2] Patients were followed for 2 years.[2] This open-label, phase 2 study evaluated the effect of teplizumab on C-peptide levels.[2] At 2 years, people receiving teplizumab had less reduction in C-peptide levels compared to no treatment, -0.28 mmol/L versus -0.46 mmol/L ; p=0.002), which suggests preservation of beta-cell function. However, there were no significant differences in HbA1c levels between the groups.[2]

In the phase 3 trial (PROTÉGÉ) eligible participants were diagnosed with T1D within the previous 12 weeks or less, were a mean age of 7 years and had a mean HbA1c of 8.25%.[3] Total insulin mean insulin dose was 0.65 U/kg per day at baseline.[3] During the study the investigators were advised to titrate insulin to an HbA1c of 6.5% or lower and an insulin dose of at least 0.25 U/kg per day. The dose of teplizumab was: teplizumab 14-day full dose (total dose of 9,034 mcg/m^2 over 14 days; repeated at week 26), teplizumab 14-day low dose (total dose of 2,985 mcg/m2 over 14 days; repeated at week 26), teplizumab 6-day full dose (total dose of 2,426 mcg/m2 over 6 days, followed by 8 days of placebo; repeated at week 26).[3] The composite outcome of the percentage of participants with insulin use of less than 0.5 units/kg per day and HbA1c less than 6.5% at one year.[3] Results were reported at one year as prespecified by the study protocol; however, the study duration was two years.[3] The results for the primary composite outcome were not significantly different between the teplizumab groups compared to placebo. The composite of patients with insulin use of less than 0.5 U/kg per day and HbA1c of less than 6.5% at 1 year, after 14 days of therapy, was 19.8% (n=41) for teplizumab full dose, 13.7% (n=14) for teplizumab low dose, 20.8% (n=22) for teplizumab 6-day full dose, and 20.4% (n=20) for placebo. Secondary outcome results were considered exploratory because the primary composite outcome did not reach statistical significance.

Limitations to the studies are the small sample sizes, use in predominately White populations, and strict inclusion criteria. There is consistent evidence from two studies that teplizumab does not improve outcomes in participants that have been recently diagnosed with T1D. A phase 3 study for the treatment of early-onset T1D is underway (PROTECT, NCT03875729) and may inform additional indications for teplizumab. There is insufficient evidence for a second course of teplizumab; however this is being evaluated in ongoing studies.

Clinical Safety:
Common adverse reactions experienced with teplizumab are presented in **Table 3**.[4] Teplizumab is associated with CRS which occurred in 2% of participants in trials compared to 0.0% of placebo treated participants.[4] Teplizumab should be discontinued in those people who have liver enzyme elevations 5 times of upper limit of normal. If severe CRS occurs, pausing dosing should be considered. Teplizumab should not be used in people with serious or chronic infection and teplizumab should be discontinued if a serious infection occurs. Serious infections (e.g. cellulitis, gastroenteritis, pneumonia, and wound infection) occurred in 9% in people taking teplizumab versus 0% in people taking placebo, during treatment and through 28 days after the last dose of study drug was given.[4] Lymphopenia has been associated with teplizumab use and should be discontinued in severe lymphopenia (<500 cells/μL) that persists for 1 week or longer. The average largest reductions in lymphocyte counts occurred at 5 days with return to baseline levels at week 6. Anemia has been associated with teplizumab compared to placebo, occurring in 27% and 23% of patients, respectively. Thrombocytopenia occurred in 13% of teplizumab treated patients and in 5% of those taking placebo.[4] Rash was a common, though generally not serious, adverse reaction and often would spontaneously resolve. Age-appropriate vaccines should be given to all people taking teplizumab before initiation of therapy. Teplizumab may cause fetal harm and patients should be advised to take appropriate precautions up to 30 days before becoming pregnant and during pregnancy.

Results from an open-label extension study of Protégé are available. However, the FDA determined that limited conclusions could be drawn from this data due to dramatic differences in follow up between teplizumab and placebo groups with a 1.4-fold longer median follow-up time in the teplizumab group.

Table 3. Teplizumab Adverse Reactions in Adult and Pediatric Patients Occurring in 5% or more of Patients.[4]

Adverse Reaction	Placebo (n=32)	Teplizumab (n=44)
Lymphopenia	6%	73%
Rash	0%	36%
Leukopenia	0%	21%
Headache	6%	11%
Neutropenia	3%	5%
Increased alanine aminotransferase	3%	5%
Nausea	3%	5%
Diarrhea	0%	5%
Nasopharyngitis	0%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) T1D diagnosis
2) Time to T1D diagnosis
3) HbA1c
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Median time to progression to clinical T1D
2) C-peptide levels
3) Composite outcome of daily insulin use and HbA1C levels below specified thresholds

Table 4. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	Binds to CD3 (a cell surface antigen on T-lymphocytes). Partial agonistic signaling and deactivation of pancreatic deactivation beta cell autoreactive T lymphocytes. Teplizumab increases the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.
Oral Bioavailability	NA
Distribution and Protein Binding	2.27 L
Elimination	Not described
Half-Life	4.5 days
Metabolism	Catabolic pathways into small peptides

Abbreviations: L – Liter; NA – not applicable

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Herold, et al[1] DB, Phase 2, PC, RCT	1. Teplizumab 51 mcg per square meter of body surface area on day zero, 103 mcg/m^2 on day one, 207 mcg/m^2 on day two, 413 mcg/m^2 on day three, 826 mcg/m^2 on days four through 13. Doses given as an IV infusion 2. Saline IV infusion Median follow-up: 745 days (2 years)	Demographics: Median age: 13.5 years Male: 55% Median HbA1c: 5.3% Median glucose: 160 mg/dL[2] Sibling with T1D: 57% White: 97% Key Inclusion Criteria: - Non-diabetic relatives of people with T1D - Ages 8 years to 45 years - At high risk for development of diabetes - Two or more diabetes related autoantibodies detected in two samples obtained within 6 months before randomization - Evidence of dysglycemia* during an OGTT Key Exclusion Criteria: - Clinically important medical histories - Abnormal laboratory chemical values - Abnormal blood counts (n=76)	ITT: 1. 44 2. 32 PP: 1. 41 2. 28 Attrition: 1. 3 (7%) 2. 4 (12%)	Median time to progression to clinical T1D based on OGTT : 1. 48.4 months 2. 24.4 months HR 0.41 (95% CI, 0.22 to 0.78) p-value = 0.006 Secondary Endpoint: T1D Diagnosis at year 1: 1. 3 (7%) 2. 14 (44%) HR 0.13 (95% CI, 0.05 to 0.34) P-value not provided	NA 37%/ 3	Dermatologic or skin (rash): 1. 16 (36%) 2. 1 (3%) Blood or bone marrow (lymphopenia): 1. 33 (75%) 2. 2 (6%) Infection: 1. 5 (11%) 2. 3 (9%) Pain: 1. 5 (11%) 2. 3 (9%) Cytokine Release Syndrome: 1. 1 (2%) 2. 0 (0%) Discontinuations due to adverse events: 1. 3 (7%) 2. 4 (13%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1 and stratified by those less than 18 years and those 18 and over. Randomization numbers and tables were done by the trial coordinating center. All participants in the teplizumab group were White compared to 93.8% in the placebo group. There were 15% more participants in the placebo group that were under the age of 18 years. Performance Bias: (low) Double-masked. Differences in adverse event rates could lead to unblinding. Detection Bias: (low) Efficacy and safety analysis was done by an independent medical monitor. Attrition Bias: (low) Attrition rates were low in both groups. Results were measured via ITT analysis and missing data will be assumed to be missing completely at random (MCAR) and no method will be used to impute missing data. Reporting Bias: (high) Due to slower than expected enrollment, the protocol was changed to detect a 60% lower risk of T1D in the teplizumab compared to placebo (instead of 50%) resulting in enrollment of 71 participants compared to 144. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to young adolescents that are White. The majority of patients were less than 18 years of age in the teplizumab and placebo groups, 66% and 81%, respectively which is consistent with age of onset for T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D. Outcomes: Time to development of T1D is an appropriate outcome for a therapy used for this purpose. Setting: Thirty one sites in the United States, Canada, Australia and Germany.

2. Herold, et al[2] AbATE Phase 2, OL, RCT	1. Teplizumab*: 51 mcg/m^2 on day zero, 103 mcg/m^2 on day two, 206 mcg/m^2 on day three, 413 mcg/m^2 on day four, 826 mcg/m^2 on days five thru 14. Doses given as an IV infusion at diagnosis and after 1 year. 2. No infusion given/no treatment * Ibuprofen, diphenhydramine and acetaminophen premedication given for infusion-related reactions	Demographics: Median age: 12 years Male: 59% Time since diagnosis: 39 days Median HbA1c: 7.6% C-peptide AUC: 0.695 mmol/L Key Inclusion Criteria: - Ages 8 years to 30 years - Diagnosed with T1D within 8 weeks of study enrollment - Positive for anti-GAD65, anti-ICA512 or ICA. Key Exclusion Criteria: - Not described	mITT: 1. 56 2. 27 PP: 1. 52 2. 25 Attrition: 1. 4 (7%) 2. 2 (7%)	C-peptide levels at year 2: 1. -0.28 mmol/L (95% CI, -0.36 to -0.20) 2. -0.46 mmol/L (95% CI, -0.57 to -0.35) HR not provided P=0.002 Secondary Endpoints: HbA1C levels at year 2: 1. 7.5% 2. 7.7% (no CI provided) P=0.093	NA for all	Dermatologic or skin (rash): 1. 43 (83%) 2. 2 (8%) Blood or bone marrow (lymphopenia): 1. 1 (2%) 2. 0 (0%) Upper respiratory tract infection: 1. 32 (62%) 2. 14 (56%) Abdominal Pain: 1. 23 (44%) 2. 6 (24%) Cytokine Release Syndrome: 1. 5 (10%) 2. 0 (0%) Discontinuations due to Adverse Events: 1. 12 (21%) 2. 0 (0%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 2:1 within randomly ordered blocks of six or three. More people in the placebo group compared to teplizumab were male, 64% vs. 53.8%. Performance Bias: (high) Trial was open-label. Laboratory personnel were masked to treatment assignments. Detection Bias: (unclear) Not described. Attrition Bias: (low) Attrition rates were low in both groups. Results were measured via ITT analysis and missing data for the primary endpoint was imputed as zero if previous value was zero and if the value was more than zero then values among those in the same arm were regressed on AUC values from the prior time point. Reporting Bias: (high) Study was conducted per protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results applicable to patients with early stage 3 T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: No comparator given. Lack of comparator may bias results. Outcomes: C-peptide levels are an appropriate indicator of insulin production; however levels indicative of time to disease progression are unknown. Setting: Six study sites in North America.

3. Sherry, et al[3] PROTÉGÉ DB, MC, Phase 3, PC, RCT	1. Teplizumab 14-day full dose (total dose of 9,034 mcg/m^2 over 14 days) Repeated at week 26 2. Teplizumab 14-day low dose (total dose of 2,985 mcg/m2 over 14 days) Repeated at week 26 3. Teplizumab 6-day full dose (total dose of 2,426 mcg/m2 over 6 days, followed by 8 days of placebo) Repeated at week 26 4. Placebo * All participants were managed with exogenous insulin for T1D Trial duration: 2 years	Demographics: Mean age: 19 years Male: 63.5% Mean HbA1c: 8.25% White: 71% Key Inclusion Criteria: - Age 18 to 35 years - Body mass ≥36 kg - ≤ 12 weeks of diagnosis for clinical T1D and requirement for exogenous insulin (stage 3) - Detectable fasting or stimulated C-peptide - Positive for antibody titers against ICA-512/IA-2, GAD-65 or insulin ≤ 2 weeks of starting insulin therapy Key Exclusion Criteria: - Comorbid disorders that could affect trial outcomes or safety - Recent participation in a clinical trial - Recent vaccination - Pregnancy N=516	ITT: 1. 207 2. 102 3. 106 4. 98 PP: 1. 162 2. 79 3. 82 4. 87 Attrition: 1. 45 (22%) 2. 23 (23%) 3. 24 (23%) 4. 11 (11%)	Composite of percentage of patients with insulin use of less than 0.5 U/kg per day and HbA1c of less than 6.5% at 1 year: 1. 41 (19.8%) 2. 14 (13.7%) 3. 22 (20.8%) 4. 20 (20.4%) CI and p-values not provided Secondary Endpoints: Endpoints were considered exploratory because primary outcome was not significant, as prespecified in the protocol	NA for all	Dermatologic or skin (rash): 1. 117 (56%) 2. 58 (57%) 3. 56 (53%) 4. 21 (21%) Cytokine Release Syndrome: 1. 12 (6%) 2. 2 (2%) 3. 8 (8%) 2. 0 (0%) Blood or bone marrow (lymphopenia): 1. 181 (87%) 2. 88 (86%) 3. 85 (80%) 4. 51 (52%) Infection: 1. 94 (45%) 2. 53 (52%) 3. 55 (52%) 2. 54 (55%) Gastrointestinal disorders: 1. 71 (34%) 2. 31 (30%) 3. 44 (42%) 4. 26 (26%) Discontinuations due to adverse events: 1. 11 (5%) 2. 4 (4%) 3. 2 (2%) 2. 1 (1%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Patients were randomized 2:1:1:1 by an interactive telephone system according to a computer-generated block randomization by third party organization. Baseline characteristics were well matched. Performance Bias: (low) Medication were made using a double-dummy design and dosing was double blind. Detection Bias: (low) Data analysis was done by an independent data monitoring committee. Attrition Bias: (unclear) Attrition was high in all teplizumab treatment groups. More patients in treatment groups had missing data compared to placebo. Participants with missing data were designated as non-responders. Reporting Bias: (low) Study conducted according to protocol. Other Bias: (high) Funded by industry. **Applicability**: Patient: Results are most applicable to young adults who are White with a recent diagnosis of T1D. Intervention: Teplizumab dose was appropriate based on previous studies. Comparator: Placebo comparison appropriate since there are no other therapies approved for delaying T1D. Outcomes: Composite of insulin use and A1c appropriate to evaluate clinically significant disease progression. Setting: Eighty-three medical centers in North America, Europe, Israel and India.

Key: * Dysglycemia defined as fasting glucose level of 110 to 125 mg/dL, 2-hour post-prandial plasma glucose level of at least 140 mg per dL and less than 200 mg per dL or an intervening postprandial glucose level at 30, 60, or 90 minutes of greater than 200 mg per dL on two occasions, within 52 days before enrollment. The protocol was amended to include participants younger than 18 who had a single abnormal OGTT because rates of progression to T1D was similar with or without a confirmatory OGTT.
Abbreviations: AUC = area under the curve; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; GAD = glutamic acid decarboxylase; ITT = intention to treat; ICA = islet-cell antigen; IV = intravenous; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OGTT = oral glucose tolerance test; PC = placebo-controlled; PP = per protocol; T1D = type 1 diabetes.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TZIELD safely and effectively. See full prescribing information for TZIELD.

TZIELD™ (teplizumab-mzwv) injection, for intravenous use
Initial U.S. Approval: 2022

---------- INDICATIONS AND USAGE----------

TZIELD is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D (1).

----------DOSAGE AND ADMINISTRATION----------

- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available (2.1).
- In patients who meet criteria for a diagnosis of Stage 2 type 1 diabetes, ensure the clinical history of the patient does not suggest type 2 diabetes (2.1).
- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests. Use of TZIELD is not recommended in patients with certain laboratory abnormalities (2.2).
- Must dilute TZIELD in 0.9% Sodium Chloride Injection, USP. See full prescribing information for detailed preparation and administration instructions (2.3, 2.4, 2.5).
- Premedicate with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic before each TZIELD dose for at least the first 5 days of the 14-day treatment course (2.3).
- Administer TZIELD by intravenous infusion (over a minimum of 30 minutes) once daily for 14 days. See full prescribing information for the dosing schedule (2.4).

---------- DOSAGE FORMS AND STRENGTHS----------

Injection: 2 mg per 2 mL (1 mg/mL) single-dose vial (3).

---------- CONTRAINDICATIONS ----------

None. (4).

---------- WARNINGS AND PRECAUTIONS ----------

- *Cytokine Release Syndrome (CRS):* Premedicate, monitor liver enzymes, discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal, and if severe CRS develops consider temporarily pausing dosing (5.1).
- *Serious Infections:* Use of TZIELD is not recommended in patients with active serious infection or chronic infection. Monitor for signs and symptoms of infection during and after TZIELD treatment. If a serious infection develops, discontinue TZIELD (5.2).
- *Lymphopenia:* Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD (5.3).
- *Hypersensitivity Reactions:* If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly (5.4).
- *Vaccinations:* Administer all age-appropriate vaccinations prior to starting TZIELD. See recommendations regarding live-attenuated, inactivated, and mRNA vaccines (2.2, 5.5).

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia and headache (6.1).

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm (8.1).
- Lactation: A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration (8.2).

To report SUSPECTED ADVERSE REACTIONS, contact Provention Bio at 1-844-778-2246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

Teplizumab

Goal(s):

- To optimize the safe and effective use of teplizumab for *prevention* of type 1 diabetes mellitus (T1DM).

Length of Authorization:

- One 14-day treatment course.

Requires PA:

- All provider-administered and pharmacy point-of-sale claims for teplizumab

Covered Alternatives:

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

Approval Criteria		
1. Is the request for an FDA approved age (e.g. 8 years of age or older)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Has the patient previously been treated with teplizumab (use beyond the original 14 day infusion)?	**Yes:** Pass to RPh. Deny; medical appropriateness. No evidence to support additional doses.	**No:** Go to #3
3. Is the medication prescribed by or in consultation with an endocrinologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Have baseline liver function tests and complete blood panel been evaluated in the past 2 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age based on provider attestation of immunization history? Note: - Teplizumab labeling recommends administration of live-attenuated vaccines at least 8 weeks prior to treatment and inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. - Routine vaccinations for patients at least 8 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document provider attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the person at high risk of developing T1DM (e.g. Stage 2 diabetes) as determined by having ALL of the following: - Presence of two or more diabetes-related autoantibodies (e.g. insulin autoantibodies (IAA), islet cell antibodies (ICA), glutamic acid decarboxylase 65 (GAD) autoantibodies, insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A)) AND - Abnormal glucose tolerance during an oral glucose-tolerance test (OGTT) confirmed within the last 2 months Note: Teplizumab is preventative therapy and not approved at this time for people diagnosed with symptomatic T1DM (e.g. Stage 3)	**Yes:** Approve for one 14-day course.	**No:** Pass to RPh. Deny; medical appropriateness.

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Targeted Class Review: Growth Hormones for Adults

Date of Review: April 2023 **End Date of Literature Search:** 12/02/2022

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Review:
A comprehensive review of growth hormone therapy in adults has not previously been completed for Pharmacy and Therapeutics (P and T) Committee assessment. This drug class update examines comparative evidence for safety and efficacy of various growth hormone preparations in the management of adult growth hormone deficiency and other FDA-approved indications in adults.

Plain Language Summary:

- Hormones are important chemicals that carry messages throughout the body through the blood to organs, muscles, and other tissues. Growth hormone (GH) is natural hormone released by a gland in the brain that helps children grow, helps adults maintain a normal body structure, and plays a role to support the body's ability to build up and break down substances needed to keep children and adults healthy. People who do not naturally make enough growth hormone due to a medical condition may be diagnosed with growth hormone deficiency (GHD). Growth hormone may be used as a medicine in people that do not make enough in their own body naturally. Growth hormone medication is approved by the Food and Drug Administration to treat specific medical conditions that affect a person's ability to grow and develop. Growth hormone medication should be prescribed by a doctor with special training for treating children and adults with a medical condition that would benefit from growth hormone treatment.
- Other medical conditions besides GHD have been treated with GH. The purpose of this document is to review the medical evidence that supports the possible benefits and harms of GH therapy in adults who may need GH therapy to treat their medical condition.
- In adults with GHD, there is conflicting evidence that shows GH therapy benefits the heart, increases bone strength, improves fitness level, or leads to a better quality of life (QoL) over a long period of time compared to no treatment.
- In adults with short bowel syndrome who need a special diet, there may be some benefit compared to placebo that GH treatment may lower body fat, improve their amount of muscle tissue, and help them get better nutrition.
- In patients with Prader-Willi syndrome or HIV associated wasting/cachexia, there was not enough evidence available to decide whether GH therapy improves long-term health outcomes.
- A guideline published by the National Institute for Health and Care Excellence (NICE) for Human growth hormone (somatropin) in adults with GHD continues to recommend that:
    - GH medicine should only be used for patients with severe GHD, if needed to improve their quality of life, and if they are already receiving other hormone treatments.

- After starting a patient on GH medicine, wait 9 months then decide if the patient should continue. Doctors should not stop treatment if it is still helping improve the patient's quality of life.
- If a patient was treated for GHD as a child and then is finished growing, only continue GH medicine if needed to treat severe GHD, to improve their quality of life, and if they are already receiving other hormone treatments.
- Patients who start to lose GH in early adulthood, after they are done growing but before the age of 25 years, should be given GH treatment until their adult bone mass has peaked.[4]
- Only a doctor with special training should start a patient on GH medicine for GHD. Therapy may be continued by the patient's regular doctor only when there is there has been a discussion with the prescriber who first started the patient on the medicine.

- There is not enough evidence to recommend the use of one type of GH medicine over another.
- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of growth hormone medicine.

Research Questions:

1. What is the comparative evidence assessing efficacy of growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader Willi syndrome?
2. What is the comparative evidence assessing long term safety and harms of growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader-Willi syndrome?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by growth hormone agents for the treatment of adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader-Willi syndrome?

Conclusions:

- There are 3 systematic reviews and one high quality clinical practice guideline included in this review.
- There is insufficient comparative evidence based on one systematic review to assess whether GH therapy for adult GHD results in long-term improvements in glucose metabolic parameters, cardiovascular disease risk factors, body composition, bone structure, or health-related quality of life.[1]
- A Cochrane review found low quality evidence for patients with short bowel syndrome who were dependent upon parenteral nutritional support that GH treatment resulted in a statistically significant increase in lean body mass (LBM) compared to placebo either with or without glutamine (Mean difference (MD) 1.93 kg; 95% Confidence Interval (CI) 0.97 to 2.90; P = 0.0001; 3 studies).[2] The clinical relevance of this magnitude of change is unknown.
- The Health Evidence Review Commission (HERC) has allowed limited appropriate use of GH for adults.[3] There was insufficient evidence to draw conclusions on the impact of GH therapy on significant adverse events in adults with growth hormone deficiency, HIV-associated cachexia, short bowel syndrome, or Prader Willi syndrome.
- A guideline published by the National Institute for Health and Care Excellence (NICE) for administration of human growth hormone (somatropin) in adults with GHD continues to recommend the following:[4]
  - Initiate GH treatment only if severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies.[4]
  - Re-assess GH treatment 9 months after initiation and discontinue if there is an insufficient improvement in QoL.[4]
  - Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved.
  - After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on initiation criteria (severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies).

- Initiate GH treatment for GHD only by a qualified specialist (e.g. endocrinologist) and continue in primary care only with an agreed upon shared-care protocol.[4]
- There is insufficient evidence to recommend the use of a specific formulation of GH in preference to another.
- Additional comparative studies evaluating the effectiveness and safety of GH therapy in the adult Medicaid population are needed.

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on the review of current evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
In December 2022, prior authorization (PA) criteria for the growth hormone class was updated to align fee-for-service PA criteria with new Health Evidence Review Commission (HERC) guidance for use of human growth hormones (HGH) and their FDA-approved indications.[3] HGH is supplied in several formulations for the treatment of a limited number of pediatric and adult conditions (see **Appendix 1** for representative agents). HERC recently updated its guidance to allow limited coverage of HGH for adults and allow individualized review for HGH needs for children.[3]

Background:
Growth hormone, or somatotropin, is a polypeptide hormone released from somatotroph cells in the anterior pituitary that is commonly associated with linear growth during childhood and adolescence.[5,6,7] Metabolic processes throughout adult life are augmented by GH including the reduction of glucose utilization in peripheral tissues and stimulation of lipolysis.[5,6,7] Growth hormone triggers protein synthesis in a wide range of bodily tissues to increase muscle mass and stimulate bone formation.[5,6,7,8]

Adult Growth Hormone Deficiency (AGHD) is rare clinical syndrome that is a result of diminished GH production or tissue unresponsiveness to GH.[9] About 20% of AGHD cases may be a continuation of a childhood GH deficiency, but AGHD may also be adult-acquired.[8,9] Patients with AGHD may present with non-specific signs and symptoms such as hypertension, fatigue and decreased muscle strength, difficulty with concentration and memory, metabolic abnormalities (e.g. glucose intolerance, elevated triglycerides, increased visceral fat, impaired lipid metabolism, etc.), depression, and sleep impairment.[8,9] Some patients may show little to no symptoms.[9] Since many signs and symptoms of adult GHD are clinically similar to the typical adult aging process, individuals with AGHD may be unaware of this deficiency unless tested. Some of the more common clinical features of AGHD are listed in **Table 1**.

Table 1: Common Clinical Features of Adult Growth Hormone Deficiency[9]

Reported Symptoms
-Depression and fatigue, sleep and memory impairment, anxiety
-Increased fat mass; decreased LBM muscle strength
-Decreased exercise performance and cardiac capacity
-Dry skin
-Osteopenia or osteoporosis with increased risk of fracture
-Low serum HDL (mainly females), high serum TGs, impaired glucose tolerance

Abbreviations: HDL=high-density lipoprotein; HTN=hypertension; LBM=lean body mass; TGs=triglycerides

There are 6,000 new cases of adult GHD diagnosed in the United States annually with a prevalence estimated around 1:100,000.[9,10] Roughly 15% to 20% of the adult GHD cases are continued from a childhood onset of GHD[8-12] GH mutations may result in multiple pituitary hormone deficiencies or can cause isolated dysfunction. Various congenital abnormalities of AGHD may be linked to genetic mutations in transcription factors (e.g., HESX-1, LHX3/4, PIT-1, PITX-2, PROP-1), defects in the growth hormone-releasing hormone (GHRH) receptor gene, or even flaws in the GH gene itself.[11] Although adult-onset GHD cases are more common in those between 45 years of age and older, it may be acquired at any time in adulthood as a result of damage to the hypothalamic-pituitary axis via tumors (and their treatment), traumatic brain injury (TBI), or even infection.[5-7,12,13] Studies have reported that GHD affects men more frequently than women (19 cases vs 14.2 cases per million, respectively) and the disparity appears to increase with age.[9,13] GHD may be isolated or can manifest along with multiple hormone deficiencies.[6,9,13] There are no known mechanisms to prevent or screen for GHD.

The anterior pituitary secretes GH in short bursts at different periods throughout the night and daily following meals, after exercise, and during stress.[5-7] Although hypothalamic GHRH stimulates the production and release of GH, its synthesis is also regulated by other peripheral hormones such as glucocorticoids, thyroid hormone, and estrogen.[14] GH secretion tends to gradually increase in childhood and peak at puberty, then steadily decline throughout adulthood.[13,14] Obesity and hypothyroidism tend to suppress GH secretion.[15] The GH receptor may be found in numerous body organs and tissues such as the liver, muscle fat, kidneys and cartilage.[15] When the GH receptor is activated in the liver and peripheral tissues, Insulin Growth Factor (IGF)-1 is produced which promotes anabolic effects.[15] Given that GH is secreted in a pulsatile manner with oversight of complex biofeedback regulatory mechanisms, random sampling of GH levels is often of little benefit to diagnose AGHD and may even lead to false positives.[5-7] Since low serum IGF-1 levels tend to correlate with deficient GH secretion, IGF-1 measurements may have some utility in confirmation of AGHD.[13-17] However, because IGF-1 levels are often normal in adult GHD and lower levels are observed during weight loss and in liver disease, the utility of IGF-1 as a stand-alone AGHD diagnostic tool is not recommended and additional testing is typically required.[13-17]

For a definitive AGHD diagnosis, clinicians utilize provocative tests.[13-15,18] Provocative tests are typically warranted for patients with a high GHD probability (e.g. childhood onset GHD, post irradiation hypothalamic-pituitary disease, TBI, etc.) and are based on a maximal GH response to a stimulation test.[13-15,18] Two of the more common AGHD diagnostic tests are the insulin tolerance test (ITT) or a glucagon stimulation test.[13-15,18] The ITT is the most frequently employed test and requires a GH response of <3-5mcg/L for a GHD diagnosis.[13-15,18] However, the ITT may be cumbersome to perform, and its use is contraindicated in patients with coronary artery disease (CAD), those with seizure risk, and the elderly because it induces hypoglycemia.[13-15,18] A stimulation test with glucagon is an appropriate alternative to the ITT stimulation test.[13-15,18] The growth hormone-releasing hormone (GHRH)-arginine test may also be used to diagnose adult GHD but there has been limited use in the United States due to reduced availability and manufacturing challenges.[15] An alternative AGHD diagnostic agent, macimorelin, is a synthetic Ghrelin receptor agonist that stimulates GH release in the pituitary and hypothalamus and has been recently approved for use in the United States.[19,20] Provocative testing for GHD may be unnecessary in adult patients who had childhood onset GHD with evidence of structural pituitary disease plus multiple hormone deficiencies since these conditions are not reversible.[5,6,13] In these individuals, clinical signs and symptoms of GHD with a low IGF-1 measurement are enough for a GHD diagnosis.[13] Imaging may identify the existence of tumors or structural defects. Before deciding whether GH replacement should be continued for an adult patient, many organizations recommend retesting with provocative tests after the completion of linear growth since roughly half the adult patients have normal GH levels and may not need additional therapy.[17,18,21,22]

Characteristics of the more common GH stimulation tests used in the United States are listed in **Table 2**.

Table 2: Provocative Tests for Adult Growth Hormone Deficiency Diagnosis[18]

Test	Procedure	Interpretation of GHD	Safety/adverse effects	Comments	Diagnostic performance
ITT	IV insulin 0.05-0.15 U/kg. Record neuroglycopenic symptoms. Blood sampling: fasting, and 20, 30, 40, and 60 min after hypoglycemia is achieved.	GH < 3-5 mg/L at every time point after hypoglycemia is achieved.	Unpleasant neuroglycopenic symptoms. Contra-indications: epilepsy, cardiovascular disease, pregnancy, age >65 years. Delayed hypoglycemia may occur.	-Adequate hypoglycemia required for validation of test. -Can simultaneously assess HPA axis -Close medical supervision required. -Poor reproducibility.	PPV 93%, sensitivity 96%, and specificity 92%.
Glucagon	1 mg (1.5 mg if >90 kg) IM Measure GH every 30 min over 4 h.	GH ≤ 3 mg/L at every time point.	Nausea, vomiting, headaches, delayed hypoglycemia, diaphoresis and abdominal cramps.	-Questionable diagnostic accuracy in subjects with high BMIs and glucose intolerance. -Requires lower BMI-dependent GH cut-points to achieve optimal specificity.	Sensitivity and specificity 100% in lean subjects.
Macimorelin	8-hour fast required; administer 0.5 mg/kg oral solution; measure at 30, 45, 60, and 90 min time points after administration.	Maximally stimulated serum GH level <2.8 ng/mL (30, 45, 60 and 90 min time points) following administration confirms the presence of adult GHD	Dysgeusia, dizziness, headache, fatigue, nausea, hunger	-Avoid concomitant use with medications known to cause QTc-interval prolongation. -Safety and diagnostic performance not established for BMI of > 40 kg/m^2. -High cost	Using a GH cutoff of 2.8 ng/mL for the macimorelin test, the sensitivity was 87% and specificity was 96%.

Abbreviations: BMI=body mass index; GH=growth hormone; h=hours; HPA=hypothalamic-pituitary-adrenal; IM=intramuscular; ITT=insulin tolerance test; IV=intravenous; kg= kilogram; L=liter; mg=milligram; min=minute; ml=milliliter; ng=nanogram; PPV=positive predictive value; U=unit.

GH replacement therapy for AGHD patients has been recommended to improve various clinical outcomes but clear evidence of benefit from high quality studies is limited in the adult population.[13-15] Nonetheless, GH treatment may be a viable option for adult GHD patients with significant clinical indicators and overt evidence of GHD from pituitary removal (or destruction) or panhypopituitarism since birth.[13-15] Some common goals of GHD treatment in adulthood are to improve the patient's metabolic and cardiovascular risk profile, body composition, bone structure, and quality of life.[22] A variety of studies have investigated the effects of GH treatment on surrogate cardiovascular markers such as serum lipoprotein profiles (e.g. LDL reduction, HDL improvement) but results have been

mixed and inconsistent.[23] For example, significant increases in lean body mass and reductions in body fat content have been observed with GH replacement therapy, but no effects on BMI were observed.[24,25] Growth hormone therapy may be associated with favorable changes in myocardial structure and function but these data are reported from mostly small, open label studies. [26-28] While there is limited evidence that GH replacement may increase markers of bone mineral density after 6 months, the effects do not appear to persist beyond 18 months of treatment.[25,29] There is no published data to confirm an association between GH therapy and pituitary tumor regrowth, but due to a concern that increased IGF-1 levels may increase risk of malignancy, GH therapy is contraindicated in patients with active malignancy or severe diabetic retinopathy. [13,22,30,31] There are a number of studies and guidelines that have explored patient psychological well-being and quality of life as an important outcome measure of GHD therapy and some studies have reported a benefit.[32-34] In a subpopulation of females with GHD and prior acromegaly, GH therapy was reported to result in QoL improvements in areas such as socialization and self-confidence after 6 months based on select questionnaires.[32] The mechanism of beneficial effect on QoL attributed to GH replacement remains elusive and no standardized QoL assessment tool has been identified.[32] It does not appear that GHD has any relationship with mortality nor does GHD replacement therapy have any evidence of benefit on mortality rate.[35]

Growth hormone replacement therapy has been utilized to treat other conditions in adults, some of which are FDA-approved (see **Table 3**). Short bowel syndrome (SBS) is a disorder caused by reduced functional surface area of the intestine that leads to decreased absorption of nutrients, fluids, and electrolytes.[36,37] SBS symptom severity is dependent upon the extent damage or loss of intestinal surface area and compensatory ability of the remaining bowel.[38] Growth hormone has been shown to influence intestinal growth, function, and result in other trophic changes.[36,37] Studies with GH therapy plus the amino acid glutamine have shown mixed success for nutrient absorption, weight gain, and for reducing parenteral nutritional needs in the treatment of SBS in adults.[2,39] Likewise, GH therapy has been used to stimulate weight gain and work output in cachexia or wasting caused by AIDS.[15,40] There is research to suggest that GH therapy induces a positive nitrogen balance with decreased fat and increased muscle mass.[15] However, when GH is administered concomitantly with protease inhibitor therapy, the risk of diabetes is increased in this population, which may be a concern.[15] The treatment of SBS and cachexia or wasting associated with AIDS are both FDA-approved indications of GH therapy.[41,42]

Table 3: FDA-approved Uses of Recombinant Growth Hormone for Adults

Condition	Etiology/Pathology	Clinical Manifestations	GH Function	Approved GH Preparations
GHD[5,9,43-50]	Impaired production of GH from congenital malformations/genetic defects or acquired causes (e.g. trauma, infection, malignancy)	Early growth failure at 6-12 months with decreased growth velocity until 3 years of age, delayed bone age, jaundice, central obesity, craniofacial abnormalities, hypoglycemia, hypothyroidism, defective primary or secondary sexual development	Decreased visceral fat, increased muscle mass, and increased exercise capacity	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Saizen™ Zomacton™
HIV Associated Cachexia[40,41]	Altered metabolism and malabsorption due to HIV infection	Weight loss, anorexia, muscle atrophy, fatigue and weakness	To increase lean body mass, body weight and improve physical endurance	Serostim™

Short Bowel Syndrome[37,42]	Reduction of functional intestinal surface area from intestinal resection or tissue damage leads to malabsorption of nutrients, fluid, and/or electrolytes.	Diarrhea, dehydration, electrolyte abnormalities, weight loss, confusion and apathy	To increase weight, lean/fat-free body mass, and nutritional absorption	Zorbtive™
Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GFR = glomerular filtration rate; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; PWS= Prader-Willi syndrome; rGH = recombinant growth hormone; SHOX = Short stature homeobox-containing gene				

Growth hormone replacement therapy has also been used to treat children with PWS as they transition to adulthood.[51] Clinical features of PWS resemble that of patients with GHD, such as short stature, increased body fat, and decreased muscle mass and strength.[51] Some studies have reported a positive effect of GH therapy on body composition and quality of life in adult patients with PWS, but due to methodological limitations of the included studies, the true effects are unknown.[51] Most studies of adults with PWS have been small, observational studies of short duration with much heterogeneity.[51] Evidence of benefit in other key areas such as BMD, BMI, and fasting glucose levels has been inconclusive.[3] The long-term benefits or harms of GH therapy in adult patients with PWS are unknown.[51]

GH replacement in adults is individualized according to age, gender, and even estrogen levels.[52] The endocrinologist may consider patient age, severity, and comorbidities when dosing of GH replacement therapy, but age-based dosing with titration tends to be favored compared to weight-based regimens due to less frequency of adverse effects.[52] Patients on oral estrogen therapy may require higher doses of GH replacement while those on testosterone replacement may need a lower GH dose due to testosterone's potentiation of GH action.[22] There is no suggested limit to the duration of GH therapy if objective benefits are observed in areas such as bone mineral density and body composition, or subjective improvements in quality of life.[22] However, guidelines suggest that if after 1 year of GH treatment no benefits are observed in key outcome measures, therapy discontinuation may be considered.[13,22] A 6-month follow up appointment is recommended for patients that discontinue GH therapy to reassess if a restart of therapy is warranted.[13,22] Standard GH dosing protocols are listed in **Table 4**.

Table 4: Standard Growth Hormone Replacement Dosing Recommendations[22]

Age or Comorbidities/Conditions	Dosing*
• <30 years • Women on oral estrogen therapy	0.4 to 0.5 mg/day (or higher for patients transitioning from pediatric treatment)
30 to 60 years	0.2 to 0.3 mg/day
• >60 years • Diabetes mellitus or prediabetes • Obesity • Previous gestational diabetes	0.1 to 0.2 mg/day
Patients transitioning from childhood to adulthood GH deficiency	Resume GH doses at 50% of the dose last used in childhood

*=see prescribing information of individual agents for FDA-approved dosing and adjustments

There are several GH replacement agents available in the United States. GH preparations are generally supplied as subcutaneous solutions either in a prefilled pen/cartridge or in a vial, as powder for reconstitution. Clinical practice guidelines do not distinguish among the various preparations of GH as there is limited evidence of differences in clinical outcomes from one brand to another.[13,22] Each formulation may have a different strength, administration device, and/or storage requirement.[16,41-50] Dosing frequency may also vary among different products and conditions.[41-50,53] The choice of preparation may be individualized based on therapeutic needs, patient response, and adherence.[41-50] A drug information summary is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

There were approximately 10 fee-for-service Oregon Health Plan Fee-for-Service (OHP-FFS) patients who received growth hormones in quarter 3 of 2022. Approximately 72% of the paid claims were for Norditropin Flexpro, 11% for Omnitrope, 11% for Genotropin, and 6% for Humatrope. Growth hormones currently represent a relatively small proportion of overall health care claims and costs to the Oregon Health Authority (OHA).

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:
CADTH Rapid Response Report - Human Growth Hormone Treatment for Adult Growth Hormone Deficiency: A Review of the Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines[1]
A 2015 CADTH review evaluated the evidence for efficacy and safety of human growth hormone for adult GHD.[1] Literature was evaluated from 2007 through 2015.[1] The intervention in the RCTs was GH replacement therapy as compared to placebo.[1] No other relevant heath technology assessments, meta-analyses, or randomized controlled trials (RCTs) were identified since the previous review.[1] Clinical outcomes included CVD risk factors, metabolic parameters, anthropometry, bone parameters, cognitive function, quality of life (QoL) and adverse events. All studies reviewed included patients with severe GHD who were 25 years of age or older.[1] Quality of the included systematic review (SR) was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[1]

One systematic review met inclusion criteria and consisted of 11 studies (N=534) 2 of which were RCTs (N=62)], in patients 60 years of age or older.[1] The RCTs had a duration of 6 and 12 months.[1] One RCT found no differences in cognition, Hemoglobin (Hb)A1c, insulin, or serum glucose with GH therapy compared to placebo.[1] One RCT reported a decrease in total cholesterol, Low-density Lipoprotein (LDL), and LDL/HDL ratio and an increase in resting heart rate with GH therapy compared to placebo.[1] However, the included studies did not quantify results or discuss statistical significance of all findings in the conclusion.[1] Adverse events reported with GH therapy use were cerebrovascular events, neoplasms, fluid retention, arthralgia, peripheral edema, and headache.[1] One RCT observed no differences in adverse events between placebo and GH therapy groups.[1] No evidence was identified to support clinical effectiveness of GH therapy for direct health impacts in

GHD patients.[1] Therefore, it was determined that evidence was insufficient to determine the safety of GHR therapy or to formulate any meaningful outcome conclusions.[1]

Wales, et al – Human growth hormone and glutamine for patients with short bowel syndrome[2]
A 2010 Cochrane systematic review and meta-analysis evaluated the role of GH treatment for patients with short bowel syndrome.[2] Five randomized controlled trials were included (n=79) with durations from 3 to 18 weeks.[2] Comparisons were between GH therapy and placebo in mostly adult patients diagnosed with short bowel syndrome and dependent on parenteral nutrition support.[2] In 4 of the studies, ages ranged from 18-75 years, while 1 study included 8 patients with a mean age of 12.9 years.[2] There were 34 males and 45 females included.[2] The primary outcome of interest was change in body weight (kg) while secondary outcomes included change in lean body mass, energy absorption, nitrogen absorption, fat absorption, carbohydrate absorption, serum IGF-1, parenteral nutrition (PN) requirements (volume/calories used or frequency of administration), and adverse events.[2]

The risk of bias was low for all of the 5 included studies.[2] Pooled estimates calculated for 3 studies found GH treatment by the end of therapy resulted in a statistically significant increase in LBM compared to placebo either with or without glutamine (MD 1.93 kg; 95% CI 0.97 to 2.90; P = 0.0001).[2] The meta-analysis of 3 trials found by the end of therapy that GH treatment resulted in a statistically significant increases in energy absorption (MD 4.42 Kcal; 95% CI 0.26 to 8.58; P = 0.04), nitrogen absorption (MD 44.85 g; 95% CI 0.20 to 9.49; P = 0.04), and fat absorption (MD 5.02 g; 95% CI 0.21 to 9.82; P = 0.04).[2] There is no minimum clinically important difference published for these outcomes so the clinical relevance of this magnitude of change is unknown.[2] For those who received GH therapy, glutamine and diet manipulation, there was a statistically significant reduction in weekly PN volume (~2 L), calories (~1400), and number of infusions (~1) required compared to GH and glutamine placebo (p<0.001). The reported reduction in PN requirements appeared to be maintained at 3 months (P<0.005).[2] There were no statistically significant changes reported in carbohydrate absorption or serum IGF-1 in the pooled analysis.[2] The most frequently reported adverse events were peripheral edema (44/57 [77%]), arthralgia (2/120 [10%]), and carpal tunnel syndrome (16/49[32%]).[2] Due to the small number of patients enrolled, the limited duration of the studies, and the short-lived effect of GH therapy, it is unclear whether GH therapy has long-term benefit in this population as any observed improvements were short-term and did not continue after therapy ceased.[2] The evidence was insufficient to recommend routine use of GH or glutamine in short bowel syndrome.[2]

After review, 15 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).

Guidelines:
High Quality Guidelines:

National Institute of Health Care Excellence (NICE) – Human growth hormone (somatropin) in adults with growth hormone deficiency[4]
NICE published guidance for the use of human growth hormone (somatropin) in adults with growth hormone deficiency.[4] Originally published in 2003, NICE reviewed the evidence again in 2014 and did not find any new information that affected the recommendations.[4] The assessment identified 17 published RCTs that evaluated the effects of GH including QoL in roughly 900 adult patients with GH deficiency.[4] Twenty-three different assessment scales were used, within a variety of trial designs.[4] The duration of the studies was typically 6 months and the number of participants ranged from 6 to 173.[4] Most studies included both adult- and childhood-onset GH deficiency.[4] Highlights of NICE treatment recommendations for patients with GHD are summarized as follows:

- Initiate GH treatment only if severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies.[4]

- Re-assess GH treatment 9 months after initiation and discontinue if there is an insufficient improvement in QoL.[4]
- Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved.[4]
- After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on initiation criteria (severe GHD, impaired QoL, or already receiving treatment for any other pituitary hormone deficiencies).[4]
- Initiate GH treatment for GHD only by a qualified specialist and continue in primary care only with an agreed upon shared-care protocol.[4]

Strengths and limitations of the evidence were not provided.

Additional Guidelines for Clinical Context:

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care[22]

A 2019 practice guideline on the management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care was released by American Association of Clinical Endocrinologists and American College of Endocrinology. [22] The guideline used a clinical practice guideline algorithm and checklist process detailed in a previous publication, but no comprehensive search strategy was recorded.[22] The authors, including the Task Force Chair, revealed numerous conflicts of interest with various manufacturers and no systematic methods were detailed in the evidence search strategies. Therefore, the results are included solely for clinical context purposes.[22]

Recommendations were assigned a grade (A=very strong; B=strong; C=not strong; D=primarily based on expert opinion) with a numerical value based on best level of evidence (LOE): 1=strong [e.g. RCTs and meta-analysis of only RCTs], 2=intermediate [e.g. non-randomized or observational studies], 3=weak [e.g. case reports and economic studies], or 4=no evidence [e.g. theory or opinion].[22] The strongest recommendations in clinically important areas based on evidence from RCTs or meta-analysis of only RCTs may be summarized as follows:

Childhood-Onset GHD (CO-GHD) versus Adult-onset GHD (AO-GHD)

- Clinicians should recognize etiology of GHD as CO-GHD occurs during the developmental years and adults with CO-GHD may have had a longer duration of being GH-deficient than their AO-GHD counterparts (Grade A; LOE 1).

Continuing GH Replacement Therapy

- Adults with childhood-onset GHD caused by structural pituitary abnormalities or brain tumors should be followed up closely during transition due to more risk markers than those with adult-onset GHD (Grade A; LOE 1).[22]
- Resume GH replacement therapy in patients with confirmed persistent GHD (e.g. determined by GH-stimulation testing, or in those with multiple pituitary hormone deficiencies and structural pituitary abnormalities or brain tumors and/or genetic mutations) during transition period after final height achieved due to evidence of long-term improvement in body composition, bone health, quality of life, and lipid metabolism in adulthood (Grade A; LOE 1).[22]

Adult GHD Testing

- GH-stimulation test(s) is recommended during transition for patients with idiopathic isolated GHD and serum IGF-1 SDS <0, when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric GH therapy (Grade A; LOE 1).[22]

- The insulin tolerance test (ITT) remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of 5 mg/L. The ITT is increasingly used less frequently in the U.S. because of safety concerns, laboriousness, potential to cause severe hypoglycemia, and contraindicated in certain patients, such as elderly patients and those with seizure disorders and cardiovascular or cerebrovascular disease. The glucagon-stimulation test (GST) could be considered as an alternative test (Grade B; LOE 1).[22]

Monitoring GH Replacement Therapy

- Individualize GH therapy dosing independent of body weight, starting with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects (Grade A; LOE 1).[22]
- Initiate GH therapy using low GH dosages (0.1 to 0.2 mg/day) in GH-deficient patients with concurrent DM, obesity, older age, and previous gestational DM to avoid impairment of glucose metabolism. Higher GH therapy starting doses (0.3 to 0.4 mg/day) are advised in nondiabetic young adults <30 years of age and women on oral estrogen therapy (Grade A; LOE 1).[22]
- After starting on GH therapy, it is recommended to follow patients at 1- to 2-month intervals initially, increasing the GH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. Once maintenance doses are achieved, follow-up at approximately 6- to 12-month intervals. Shorter follow-up time intervals and smaller dose increments can be implemented especially for the elderly, and those with other comorbidities, such as DM (Grade A; LOE 1).[22]
- Monitor for interactions of GH with glucocorticoid and/or thyroid hormones. Dose adjustments for these agents may be required especially upon GH therapy initiation; less frequent monitoring may be undertaken once stable doses established unless symptoms develop, or radiotherapy administered (Grade B; LOE 1).[22]

GH Replacement Side Effects

- Reduce dose or stop therapy to manage fluid retention; use lower doses in obese and older patients who are more susceptible to side effects (Grade A; LOE 1).[22]
- Avoid use of high doses of GH therapy to minimize side-effects and target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between –2 and + 2) (Grade A; LOE 1).[22]

Long-term Safety of GH Therapy

- If DM develops during GH therapy, or if GH therapy is considered in patients with concurrent DM, use of low-dose GH therapy, and addition and/or adjustments in antidiabetic medications are suggested. If DM worsens, it is reasonable to initiate or increase the doses of antidiabetic therapy or discontinue GH therapy and optimize treatment of DM first before considering resuming GH therapy in these patients (Grade B; LOE 1).[22]

GH Therapy for Sports and Anti-Aging

- Drug testing of GH abuse via urine sampling not accurate or reliable, and 24-hour blood sampling not practical nor feasible in sports setting (Grade A; LOE 1).[22]
- In the U.S., off-label distribution or marketing of GH for the enhancement of athletic performance or to treat aging or aging-related conditions is illegal and punishable by imprisonment. Under no circumstances should GH be prescribed for sports or for “anti-aging” purposes (Grade A; LOE 1).[22]

<u>Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline</u>[54]

The Endocrine Society created practice guidelines for hormonal replacement in hypopituitarism. The guidelines were developed through a Clinical Guidelines Subcommittee Task Force.[54] Strength of recommendations were either strong (1) or weak (2), while quality of evidence graded on a 4-point scale as high- (4+), moderate- (3+), low- (2+) or very low-quality (1+).[54] Details regarding the search strategy or the criteria for the evidence selection was not described. [54] Multiple

authors including the Task Force Chair had significant conflicts of interest and it was not disclosed whether the views or interests of the funding body influenced the final recommendations.[54] Therefore, the guidelines will be used for clinical context only. In GHD therapy, there following were strong recommendations with at least moderate quality evidence:

- In patients with suspected GH deficiency (GHD), we recommend GH stimulation testing. Single GH measurements are not helpful. (Strong recommendation; moderate quality evidence)[54]
- Offer GH replacement to those patients with proven GHD and no contraindications. We recommend a starting dose of 0.2– 0.4 mg/d for patients younger than 60 years and 0.1– 0.2 mg/d for patients older than 60 years. (Strong recommendation; moderate quality evidence)[54]

Endocrine Society 2011 – Evaluation and Treatment of Adult GHD[13]

The Endocrine Society published practice guidelines developed from a Clinical Guidelines Subcommittee Task Force for guidance on the evaluation and treatment of adult GHD.[13] The Task Force used the GRADE system to describe the strength of recommendations and the quality of evidence.[13] Strength of recommendations were denoted as strong (1) or weak (2), while quality of evidence was graded on a 4-point scale which ranged from high quality (4+) to very low quality (1+).[13] Details regarding the search strategy or the criteria for the evidence selection was not described. Multiple authors including the Task Force Chair had significant conflicts of interest and it was not disclosed whether the views or interests of the funding body influenced the final recommendations.[13] Therefore, the guidelines will be used for clinical context only.

Table 6: Endocrine Society Clinical Recommendations for Evaluation and Treatment of Adult GHD (modified)[13]

Recommendation	Strength	Quality of Evidence
GHD Definition in Adults		
Patients with childhood-onset GHD who are candidates for GH therapy after reaching adult height should be retested for GHD (unless deficiencies from known mutations or structural pituitary lesions/damage)	Strong	High
Adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies be considered for evaluation for acquired GHD	Strong	High
Use two GH stimulation tests before making the diagnosis of idiopathic GHD	Weak	Very low
GHD Diagnosis		
Insulin tolerance test (ITT) and the GHRH-arginine test have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, GHRH-arginine test may be misleading in those with clearly hypothalamic causes of suspected GHD	Strong	High
Use glucagon stimulation test to diagnose GHD when GHRH test not available and ITT is either contraindicated or not practical	Weak	Low
A low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing	Strong	Moderate
A normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD	Strong	High
A low IGF-I level, in the absence of catabolic conditions, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing	Strong	Low
Deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context, provocative testing is optional	Strong	Moderate

GHD Consequences and GH Treatment Benefits		
GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity	Strong	Moderate
GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity	Weak	Low
After documentation of persistent GHD, GH therapy should be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period	Strong	Low
GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes (e.g. lipoprotein metabolism) but tends to increase insulin resistance	Weak	Low
GH has not yet been shown to improve mortality	Weak	Very Low
GH therapy of GH-deficient adults improves the quality of life of most patients	Weak	Low
Side Effects and Risks Associated with GH Therapy		
GH treatment is contraindicated in the presence of an active malignancy	Strong	Very Low
GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications	Strong	Moderate
Thyroid and adrenal function should be monitored during GH therapy of adults with GHD	Weak	Low
Treatment Regimens		
GH dosing regimens should be individualized rather than weight-based; start with low doses titrate to clinical response, side effects, and IGF-I levels	Strong	High
GH dosing should take gender, estrogen status, and age into consideration	Strong	High
During GH treatment, patients should be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response	Weak	Low

After review, 2 additional guidelines were excluded due to poor quality.[55,56]

Randomized Controlled Trials:
A total of 1775 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
somatropin	GENOTROPIN	CARTRIDGE	Y
somatropin	GENOTROPIN	SYRINGE	Y
somatropin	NORDITROPIN FLEXPRO	PEN INJCTR	Y
somatropin	NUTROPIN AQ NUSPIN	PEN INJCTR	N
somatropin	HUMATROPE	CARTRIDGE	N
somatropin	HUMATROPE	VIAL	N
somatropin	NORDITROPIN	CARTRIDGE	N
somatropin	OMNITROPE	CARTRIDGE	N
somatropin	OMNITROPE	VIAL	N
somatropin	SAIZEN	VIAL	N
somatropin	SAIZEN-SAIZENPREP	CARTRIDGE	N
somatropin	SEROSTIM	VIAL	N
somatropin	ZOMACTON	VIAL	N
somatropin	ZORBTIVE	VIAL	N
lonapegsomatropin-tcgd	SKYTROFA	CARTRIDGE	N

Appendix 2: Clinical Pharmacology and Pharmacokinetics. [41-49,53]

Somatropin	Mechanism of Action: Polypeptide hormone produced through recombinant DNA technology that promotes skeletal, visceral and general body growth, stimulates protein anabolism, and affects fat and mineral metabolism.					
Formulation (manufacturer)	Absorption	Metabolism/ Excretion	Half life (hours)	C-max	AUC	Vd
Genotropin®[43] (Pfizer, Inc)	80%	Catabolism in both liver and kidneys; 0.3 L/hr/kg	3	17.4 (± 9.2) ng/mL to 23.0 (± 9.4) ng/mL	Not reported	1.3 L/kg
Norditropin®[45] (Novo Nordisk, Inc.)	N/A	Liver and kidneys; N/A	7-10	17.1 (±10.0) ng/mL to 13.8 (±5.8) ng/mL	Not reported	43.9 L
Nutropin AQ® [46] (Genentech, Inc.)	81%	Liver and kidneys; 116−174 mL/hr/kg	2.1 ± 0.43	71.1 µg/L	677 µg•hr/L	50 mL/kg
Humatrope®[44] (Lilly USA, LLC.)	75%	Liver and kidneys; 0.18 L/hr/kg	3.8	63.3 ng/mL	Not reported	0.96 L/kg
Omnitrope®[47] (Sandoz, Inc.)	N/A	Liver and kidneys; 0.14 L/hr•kg	2.5-2.8	72-74 mcg/L	Not reported	Not reported
Zomacton®[49] (Ferring Pharmaceuticals, Inc.)	70%	Liver and kidneys; 0.133 L/min (intravenous)	2.3	38.1 ng/mL	Not reported	53.3 L
Saizen®[48] (EMD Serono, Inc.)	70 to 90%	Liver and kidneys; 14.6 ± 2.8 L/hr	2	Not reported	Not reported	12.0 ± 1.08 L
Serostim®[41] (EMD Serono, Inc.)	70 to 90%	Liver and kidneys; 0.0015 ± 0.0037 L/h	4.28 ± 2.15	Not reported	Not reported	12.0 ± 1.08 L
Zorbtive®[42] (EMD Serono, Inc.)	70 to 90%	Liver (minor); Primarily kidney; 0.0015 ± 0.0037 L/h.	4	Not reported	Not reported	12.0 ± 1L

Drug Safety Warnings/Precaution: [41-49,53]

- Growth hormone deficiency due to intracranial lesion
- Diabetes (may cause insulin resistance)
- Pituitary hormone deficiency or hypoadrenalism
- Thyroid dysfunction
- Fluid retention: Fluid retention may occur in adults; manifestations generally transient and dose dependent.
- Hypersensitivity: Serious systemic hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported.

- Intracranial hypertension: Intracranial hypertension with headache, nausea, papilledema, visual changes, and/or vomiting has been reported; symptoms usually occur within the first 8 weeks of therapy and signs and symptoms of intracranial hypertension may rapidly resolve after discontinuation or reduction of dose. Funduscopic examination prior to initiation of therapy and periodically thereafter is recommended. Patients with Turner syndrome, chronic renal impairment and Prader-Willi syndrome may be at increased risk for intracranial hypertension.
- Lipoatrophy: Lipoatrophy has been reported at injection sites when used at the same site for a prolonged period. Ensure proper injection technique and rotate injection sites.
- Neoplasm: Increased risk of malignancy progression in patients with active malignancy; preexisting malignancy should be inactive and treatment complete prior to initiating therapy. Patients with HIV and pediatric patients with short stature (genetic cause) have increased baseline risk of developing malignancies; consider risk/benefits prior to initiation of therapy and monitor these patients carefully. Rule out pituitary tumor (or other brain tumors) prior to initiation of treatment because growth hormone deficiency may be an early sign of the presence of these tumors.
- Pancreatitis: Has been rarely reported; incidence in children with Turner syndrome may be greater than adults.
- Slipped capital femoral epiphyses: Patients with endocrine disorders (including growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth may develop slipped capital femoral epiphyses more frequently; evaluate any child with new onset of limp or with complaints of hip/knee pain.

Use in Specific Populations:[41-49,53]

- Elderly: Patients with advanced age may be more sensitive to the actions of somatropin; consider lower starting doses and smaller dose increments.
- Pediatric:
    - Failure to increase growth rate, especially during the first year of therapy, indicates need for close assessment of adherence and evaluation for other causes of growth failure, such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone.
    - Childhood cancer survivors may have increased risk of intracranial tumor development
- Renal transplant recipients: use of Nutropin AQ is not indicated in patients with functioning renal allografts.
- Effects in Pregnancy/Lactation: Safety not established
- Adrenal insufficiency: Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) adrenal insufficiency with somatropin therapy; patients with previously diagnosed adrenal insufficiency may require increased glucocorticoid doses. Excessive glucocorticoid therapy may inhibit the growth-promoting effects of somatropin in children.
- Chronic kidney disease: Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy. Obtain x-rays of the hip prior to initiating somatropin in chronic kidney disease patients; be alert to the development of a limp or complaints of hip or knee pain.
- Hypothyroidism: Patients who have or are at risk for pituitary hormone deficiency(ies) may be at risk for central (secondary) hypothyroidism; patients with Turner syndrome have an increased risk of developing autoimmune thyroid disease and primary hypothyroidism. Untreated/undiagnosed hypothyroidism may decrease response to somatropin therapy, particularly the growth response in children.
- Prader-Willi syndrome: Sudden death has been reported in pediatric patients with Prader-Willi syndrome following the use of growth hormone. The reported fatalities occurred in patients with one or more risk factors, including severe obesity, history of upper airway obstruction or sleep apnea, respiratory impairment, or unidentified respiratory infection; male patients may be at greater risk. Treatment interruption recommended for patients who show signs of upper airway obstruction, including the onset of, or increased, snoring and/or new-onset sleep apnea. Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, use is not indicated for the long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.

- Scoliosis: Progression of scoliosis may occur in children experiencing rapid growth.
- Turner syndrome: Patients with Turner syndrome are at increased risk for otitis media and other ear/hearing disorders, autoimmune thyroid disease, primary hypothyroidism, and cardiovascular disorders (eg, hypertension, aortic aneurysm/dissection, stroke).

Drug Interactions:[41-49,53]
- Antidiabetic Agents: Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents.
- Corticosteroids (Systemic – prednisone, cortisone, etc): May diminish the therapeutic effect of Growth Hormone Analogs and Growth Hormone Analogs may decrease serum concentrations of the active metabolite(s) of Corticosteroids.
- Estrogen Derivatives: May diminish the therapeutic effect of Growth Hormone Analogs. Management: Initiate somapacitan at 2 mg once weekly in patients receiving oral estrogens. Monitor for reduced efficacy of growth hormone analogs; increased doses may be required.
- Macimorelin: Products that affect Growth Hormone may diminish the diagnostic effect of Macimorelin.
- Thyroid Products: Somatropin may diminish the therapeutic effect of Thyroid Products

Boxed Warnings:
There are no known boxed warnings for somatropin products.

Risk Evaluation Mitigation Strategy (REMS) Programs:
There are no known REMS programs for somatropin products.

Contraindications:[41-49,53]
- Hypersensitivity to somatropin or any component of the formulation
- Growth promotion in pediatric patients with closed epiphyses
- Acute critical illness due to increased complications/mortality following open heart or abdominal surgery
- Multiple accidental trauma, or acute respiratory failure
- Active neoplasia
- Diabetic retinopathy
- Pediatric patients with Prader-Willi syndrome
    - who have severe obesity or severe respiratory impairment (Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton)
    - who have a history of upper airway obstruction or sleep apnea (Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Zomacton)

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to December 2, 2022
1 somapacitan.mp. /23
2 somatropin.mp. /310
3 somatotropin.mp. /8265
4 humatrope.mp. /29
5 nutropin.mp. /26
6 serostim.mp. /39
7 zomacton.mp. /6
8 saizen.mp. /39
9 norditropin.mp. /97
10 zorbtive.mp. /3
11 genotropin.mp. /123
12 omnitrope.mp. /56
13 human growth hormone.mp. or Human Growth Hormone/ 20417
14 growth hormone.mp. or Growth Hormone/ 77150
15 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/ 77869
16 limit 15 to (english language and full text and humans and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "systematic review")) /3038
17 Adults.mp. or Adult/ 5755856
18 16 and 17 /1775

Appendix 4: Key Inclusion Criteria

Population	Adults with GHD, SBS, HIV Associated Wasting or Cachexia, or Prader-Willi Syndrome
Intervention	Growth hormone
Comparator	Placebo or active treatment
Outcomes	Mortality, metabolic and cardiovascular risk, body composition, bone structure, and quality of life
Timing	NA
Setting	Outpatient

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) in adults for where there is medical evidence of effectiveness and safety and supported by expert guidelines.

NOTE: Treatment with GH in children and adolescents (for any indication) are evaluated for medical appropriateness and medical necessity on a case-by-case basis.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment is not included for use in antiaging therapy or to enhance athletic ability or for body building.

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. Pediatric and Adults FDA Approved Indications for Growth Hormone

	somatropin									Lonapeg-somatropin
	Genotropin	Norditropin	Nutropin AQ	Humatrope	Omnitrope	Saizen	Serostim	Zorbtive	Zomacton	Skytrofa
Pediatric Indications										
GHD	X	X	X	X	X	X			X	X
Prader-Willi Syndrome	X	X			X					
Noonan Syndrome		X								
Turner Syndrome	X	X	X	X	X				X	

Idiopathic Short Stature	X	X	X	X	X				X	
SHOX Deficiency				X					X	
Growth Failure Secondary to CKD			X							
Small for Gestational Age	X	X		X	X				X	
HIV Associated Cachexia							X			
Adult Indications										
GHD	X	X	X	X	X	X			X	
HIV Associated Cachexia							X			
SBS								X		

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; SBS = short bowel syndrome; SHOX = Short stature homeobox-containing gene

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #3

Initial Approval Criteria		
3. Is the request for one of the conditions listed below? For children and adolescents age 17 and younger • Growth hormone deficiency (GHD) • Prader-Willi syndrome • Noonan syndrome • Turner syndrome • Idiopathic Short Stature • Growth Failure secondary to chronic kidney disease (CKD) • Small for gestational age • Short stature homeobox-containing (SHOX) gene deficiency • HIV Associated Cachexia For adults age 18 years and older • Growth hormone deficiency (GHD) • HIV Associated Cachexia • Short Bowel Syndrome (SBS)	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; medical appropriateness For current age < 21 years: Go to #5.
4. Has the provider documented goals of therapy and objective baseline assessment (e.g., quality of life, exercise capacity, height, body composition improvements, etc)? Note: these same assessments should be evaluated for continuation of treatment.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
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 #11	**No:** Pass to RPh. Deny; medical appropriateness
6. Is this a request for initiation of growth hormone therapy?	**Yes:** Go to #7	**No:** Go to **Renewal Criteria**
7. Is the agent being prescribed by, or in consultation with, an appropriate specialist (e.g., an endocrinologist for adults or a pediatric endocrinologist or pediatric nephrologist for children/adolescents)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for a pediatric patient with Prader-Willi syndrome who also has: • Severe obesity? Or • A history of upper airway obstruction or sleep apnea? Or • Severe respiratory impairment? Note: Recombinant somatropin is contraindicated in these patients due to the risk of sudden death.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Is the request for treatment of hypopituitarism (E23.0)?	**Yes:** Go to #10	**No:** Go to #11

Initial Approval Criteria		
10. Is the growth hormone deficiency confirmed by a negative response to a growth hormone stimulation test (eg, serum GH levels of <5 ng/ml on stimulation testing with either glucagon or insulin)? OR Is there evidence that the patient had the pituitary removed/destroyed or has had panhypopituitarism since birth?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
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 up to 12 months	**No:** Go to #12
12. Will the prescriber change to a preferred product that is medically appropriate for the condition? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Go to #13
13. Is the request for lonapegsomatropin?	**Yes:** Go to #14	**No:** Approve for up to 6 months
14. Is the request for a pediatric patient 1 year or older with a body weight ≥11.5 kg?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in a patient prior to reaching adulthood (<18 years of age) to improve growth velocity or height?	**Yes:** Go to #3	**No:** Go to #5
3. Is growth velocity 2 cm or more per year?	**Yes:** Go to #6	**No:** Go to #4
4. Is there documentation that benefits of therapy continue to outweigh risks? When main goal of therapy is growth promotion in children to normalize final adult height, current guidelines recommend discontinuation of treatment once growth velocity is less than 2-2.5 cm per year. Risks, benefits, and goals of therapy should be reassessed in patients whose epiphyses are closed.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of improvement from baseline as assessed by the prescribing provider?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 6 months

P&T Review: 4/23 (DE); 12/22;12/21; 6/21;11/18; 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 1/1/19; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03

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Drug Class Review: Circadian Rhythm Sleep Disorders

Date of Review: April 2023 **End Date of Literature Search:** 1/1/2007-01/03/2023

Purpose for Class Review:
To evaluate efficacy and safety of medications, including stimulants and sedating drugs, for circadian rhythm sleep disorders.

Plain Language Summary:

- People have difficulty sleeping during the night and staying awake during the day when their body's internal sleep cycle does not match their usual sleep schedule. These specific types of sleep problems are called circadian rhythm sleep-wake disorders. Examples include shift work disorder and jet lag.
- Evidence shows 2 types of medicines may help people with these types of sleep disorders:
    - Sedative medicines that help people sleep better during the night or
    - Stimulant medicines like armodafinil, modafinil, and caffeine that help people stay awake longer during the day.
- Researchers have not studied other stimulants in people with circadian rhythm sleep disorders.
- Changes in lifestyle may improve sleep problems for people with these conditions. For example, people may be more alert during the day and get better sleep when they:
    - change their exposure to bright light,
    - change the time of day that they exercise,
    - change their bedtime, or
    - plan naps during the day.
- To improve sleep, the American Academy of Sleep Medicine recommends melatonin and medicines that act like melatonin in the body for:
    - adults who are blind,
    - people who have difficulty falling asleep at night, and
    - children with conditions affecting their brain development.
- In people who have trouble staying awake at work, armodafinil and modafinil may help people avoid error during work, but they also have serious side effects including risk for heart problems, thoughts of suicide, and skin damage.
- In people who have trouble falling asleep after working a night shift, melatonin may help people sleep about 15 to 30 minutes longer compared to no treatment.
- Evidence does not show that any one medicine is better than another, or that medicine is better than lifestyle changes.
- Providers must explain to the Oregon Health Authority why someone needs a sedative or stimulant before Medicaid will pay for it. This process is called prior authorization.

Author: Sarah Servid, PharmD

- Medicaid Open Card will pay for caffeine tablets when prescribed by a provider without prior authorization. Medicaid Open Card will pay for melatonin without prior authorization when prescribed for children. Melatonin is not covered for adults.
- We recommend Medicaid continue to pay for medicines for circadian rhythm sleep-wake disorders only when necessary, on a case-by-case basis.

Research Questions:

1. What is the comparative efficacy or effectiveness of drugs (e.g., sedative hypnotics, melatonin, melatonin agonists, benzodiazepines, or stimulants) for treatment of circadian rhythm sleep-wake disorders?
2. What is the comparative safety of drugs for treatment of circadian rhythm sleep-wake disorders?
3. Are there any subpopulations who would receive more benefit or suffer more harm from drugs for treatment of circadian rhythm sleep-wake disorders (e.g., based on disease severity markers, specific types of circadian rhythm sleep-wake disorders, or comorbid conditions)?

Conclusions:

- There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
- There is insufficient evidence to support use of sedative hypnotics (e.g., zolpidem, eszopiclone, zaleplon, orexin receptor antagonists, or benzodiazepines) in people with circadian rhythm sleep-wake disorders.[1,2]
- Stimulants which have been studied for circadian rhythm sleep-wake disorders include modafinil, armodafinil, and caffeine. There is no evidence to support use of other stimulants for treatment of circadian rhythm sleep-wake disorders.
- There are no drugs currently approved by the Food and Drug Administration (FDA) for treatment of jet lag. A recent systematic review found insufficient evidence for use of pharmacologic treatments (including stimulants, sedative hypnotics, melatonin or melatonin agonists) for athletes with jet lag.[3]
- In patients with shift work disorder, melatonin and stimulants have the most evidence for use. In people with shift work disorder, there is insufficient evidence comparing efficacy or safety of melatonin, modafinil, armodafinil, and caffeine.
    - Evidence supporting efficacy of melatonin for shift work disorder is mixed. There is low quality evidence that melatonin may increase self-reported total sleep time by less than 30 minutes within 24 hours after administration in people with shift work disorder, but the clinical significance of this difference is unclear.[1] The only study which evaluated objective sleep time did not identify any differences between melatonin and placebo, and there is low quality evidence of no difference in sleep latency or sleep quality compared to placebo. [1]
    - In adults with shift work disorder and symptoms of moderate to severe excessive sleepiness, modafinil and armodafinil decreased sleepiness during the night shift (mean difference of about one point on the 9-point Karolinska Sleepiness Scale [KSS]), but was associated with more serious adverse events (9.7% vs. 2.4%; relative risk [RR] 3.97; 95% Confidence Interval [CI] 1.15 to 13.71).[1] Latency to persistent sleep during the work shift was improved by an average of 1-3 minutes compared to placebo, and remained less than 6 minutes for most patients indicating continued moderate to severe sleepiness.[4,5]
    - In shift work disorder, a 2010 Cochrane review found low quality evidence that caffeine may reduce errors at work, but there was insufficient evidence for the prevention of injuries during work.[6]
- Systematic reviews evaluating use of melatonin for sleep disorders in people who are blind have found insufficient evidence for efficacy and safety of melatonin.[7,8]
- Guidelines from the American Academy of Sleep Medicine (2015) recommend melatonin or a melatonin agonist for the following intrinsic circadian rhythm sleep-wake disorders: [2]
    - Adults, adolescents, and children with delayed sleep-wake phase disorder (low to moderate quality evidence).

- Adults who are blind and have non-24 hour sleep-wake disorder (low quality evidence).
- Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder (moderate quality evidence).
- There was insufficient evidence to inform recommendations for other treatments or other subpopulations of people with intrinsic circadian rhythm sleep-wake disorders.

Recommendations:

- Due to limited evidence of benefit for circadian rhythm sleep-wake disorders, continue to limit prescription drug use to FDA-labeled and funded indications.
- If drug treatment is medically necessary for funded circadian rhythm sleep-wake disorders or circadian rhythm sleep-wake disorders covered under EPSDT, consider coverage of a melatonin agonist or melatonin before trial of stimulants or other sedating drugs (**Appendix 4**).
- Make at least one melatonin agonist preferred. Evaluate costs of melatonin agonists in executive session.

Previous Reviews and Current Policy

- In 2020, a systematic review evaluated evidence for sleep disturbances in patients with dementia.[9] Irregular sleep-wake rhythm disorder is common in patients with neurodegenerative and neurodevelopmental disorders, though this study did not specify the specific types of sleep disorders diagnosed in this review. They identified low quality evidence that trazodone 50 mg may improve sleep efficiency and total sleep time (mean difference [MD] 42.46 minutes, 95% CI 0.9 to 84.0) with short-term treatment (2 weeks).[9] Trazodone was not included in this updated literature search for Orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (based on moderate quality evidence).[9] Other sleep outcomes demonstrated no difference from placebo. Ramelteon and melatonin did not demonstrate any change in sleep outcomes based on low quality evidence.[9] No studies evaluated other commonly prescribed therapies such as benzodiazepines or benzodiazepine receptor agonists (e.g., eszopiclone, zolpidem, zaleplon).
- A systematic review evaluating use of melatonin for sleep disorders in adults who are blind found insufficient evidence for efficacy and safety of melatonin.[7]
- Tasimelteon oral suspension was FDA approved in December 2020 for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age based on results from one small, crossover, placebo-controlled trial (n=25) evaluating treatment over 4 weeks.[10] Smith-Magenis Syndrome is a funded condition on the prioritized list. The primary outcomes were subjective total sleep time and nighttime sleep quality (reported by the patient's parent/guardian) for the 50% of nights with the worst sleep.[10] Sleep quality was rated on a 5 point scale from excellent (5) to poor (1). Compared to placebo, tasimelteon treatment resulted in improved sleep quality for the 50% of nights with the worst sleep quality though magnitude of benefit was small (2.8 vs. 2.4; least square mean difference 0.4 [95% CI 0.1 to 0.7]).[10] The difference from placebo in total sleep time for the 50% of nights with the worst sleep was not statistically improved with tasimelteon (7 vs. 6.7 hours; least square mean difference 0.3 [95% CI -0.0 to 0.6]).[10]
- In Fee for Service (FFS), all sedative drugs require prior authorization (PA). For treatment of chronic insomnia, the Health Evidence Review Commission (HERC) has recommended coverage of sedative hypnotics not exceeding 30 days every year. Melatonin is currently covered for people up to 18 years of age without PA. Melatonin is not covered for adults because it has not demonstrated improvement in symptoms compared to placebo for treatment of insomnia.
- Armodafinil and modafinil are carved-out of coordinated care organizations (CCOs) and require PA which limits use to funded conditions with documented evidence of benefit. Caffeine tablets (available over the counter) can be covered by FFS when prescribed by a provider.

Background:
Circadian rhythm sleep-wake disorders are defined as sleep disruption caused by misalignment of a person's internal circadian rhythm and the external environment.[2] The internal (or intrinsic) circadian sleep rhythm is typically slightly longer than 24 hours for most people and is synchronized (or entrained) to a 24 hour period by the 24-hour dark-light cycle and secretion of melatonin, a pineal hormone.[2] Food and exercise have a more modest effect on the circadian rhythm. Failure to synchronize to this 24-hour period can lead to circadian rhythm sleep-wake disorders.[2]

Circadian rhythm sleep-wake disorders are classified based whether on the primary driver of the disorder is internal (intrinsic) or external (environmentally-influenced).[2] For example, shift work disorder and jet lag are common circadian rhythm sleep-wake disorders that are classified as extrinsic disorders. Common intrinsic disorders include advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder, or non-24 hour sleep-wake syndrome. These are most commonly diagnosed based on clinical history, sleep logs and actigraphy. The diagnostic criteria for circadian rhythm sleep-wake disorders includes recurrent symptoms of insomnia, sleepiness or both caused by misalignment of the endogenous circadian rhythm and the individual's external environment or schedule. Polysomnography may be used to rule out other related sleep conditions, but is not usually recommended to diagnose circadian rhythm sleep-wake disorders.

Extrinsic circadian rhythm sleep-wake disorders are defined based on their external cause. Jet lag disorder is categorized as a temporary disorder related to travel across time zones creating misalignment between the desired sleep time in the new time zone and the endogenous circadian sleep-wake cycle. Symptoms typically worsen when traveling in an eastward direction and across multiple time zones. Shift work disorder occurs when a person's work schedule overlaps with usual sleep time. It is estimated that about 15% of salaried workers in the United States work on shifts including nights.[1] Shift work is generally common in younger people and prevalence varies based on the job. Some of the most common jobs that rely on shift work include healthcare and transportation industries. In people with shift work disorder, symptoms are usually present for at least 1 month and associated with functional impairment or significant distress. It is estimated that people working night shifts are more likely to fall asleep at work or experience insomnia symptoms compared to people working during the day (10% vs. 7%).[1]

Intrinsic circadian rhythm sleep-wake disorders are typically defined based on the timing of sleep and wake symptoms. Delayed sleep-wake phase disorder is characterized by a delay in the major sleep episode compared to the desired sleep schedule.[2] This results in excessive sleepiness when waking at the desired time and insomnia symptoms when trying to sleep at the desired time, but quality of sleep is typically reported as normal if sleeping on the delayed schedule. Advanced sleep-wake disorder is characterized by the opposite sleep pattern with excessive sleepiness in the evening before the individual's usual bedtime and insomnia symptoms in the early morning before the individual would normally be awake.[2] Non-24 hour sleep-wake disorder is diagnosed when an individual fails to entrain to a 24-hour cycle resulting in a gradually shifting sleep-wake pattern over time. As the internal circadian rhythm shifts, individuals experience hypersomnolence during the day and insomnia symptoms at night.[2] This is most common in individuals who are totally blind and lack external input from the 24-hour light-dark cycle. However, non-24 hour sleep-wake disorder has been documented in individuals who are sighted.[2] Irregular sleep-wake rhythm disorder does not have a clearly defined sleep-wake pattern. Symptoms typically include prolonged periods of wakefulness during the night and excessive sleepiness during the day with fragmented sleep. Irregular sleep-wake rhythm disorder is most commonly diagnosed in people with neurodevelopmental or neurodegenerative disorders.[2] For all intrinsic disorders, diagnosis typically requires documentation of sleep and insomnia symptoms for at least 7-14 days by actigraphy or sleep diary.[2]

The goal of treatment for circadian rhythm sleep-wake disorders is to realign the endogenous sleep-wake cycle with the desired external schedule to improve daytime functioning. Common outcomes evaluated in clinical trials include changes in biologic markers of circadian rhythm, total sleep time, sleep latency (or

the time it takes to fall asleep), sleep quality, and sleep onset and offset times. There are no well-established standards for minimum clinically important differences in these outcomes for people with circadian rhythm sleep-wake disorders.[2] In 2015, the American Academy of Sleep Medicine defined significance thresholds based on expert consensus that were critical for evaluating and making recommendations for intrinsic circadian rhythm sleep-wake disorders (**Table 1**).[2]

Table 1. AASM-defined clinical significance thresholds for outcomes that were critical for guideline recommendations[2]

Disorder	Change in circadian phase or total sleep time	Change in sleep onset, offset or sleep latency	Entrainment status
Advanced sleep-wake disorder Delayed sleep-wake disorder Irregular sleep rhythm disorder	30 minutes	15 minutes	N/A
Non-24 hour sleep-wake disorder	N/A	N/A	Yes/No

Abbreviation: AASM = American Academy of Sleep Medicine; N/A = not applicable

For some people total sleep time may be unchanged, but patients experience excessive sleepiness when they want to be awake, and experience insomnia symptoms when they want to sleep. In these circumstances, sleep latency and sleep onset/offset times may be a better marker of symptoms than total sleep times. Sleep quality, wakefulness, and excessive sleepiness can also be evaluated using a wide variety of tools and scales. One of the more common scales used to evaluate excessive sleepiness in circadian rhythm disorders is the Karolinska Sleepiness Scale (KSS). The KSS ranges from 1 (extremely alert) to 5 (neither alert nor sleepy) to 9 (very sleepy, great effort keeping awake).[11] There is no well-established minimum clinically important difference referenced in literature for KSS. In many clinical trials, the circadian rhythm can be evaluated using excretion of urinary or salivary melatonin concentrations (referred to as the dim light melatonin onset or the start of endogenous melatonin production during dim light conditions). However, it is not clear whether endogenous secretion of melatonin correlates well with symptoms of insomnia or function in all conditions. Several studies have evaluated dim light melatonin onset but results do not consistently correlate with improvement in symptoms of insomnia, alertness, sleep quality, or daytime function.[12] Historically, the FDA has not accepted biomarkers of urinary melatonin excretion as relevant outcomes for FDA approval of drug treatment for circadian rhythm sleep-wake disorders.[10]

Treatments for circadian rhythm sleep-wake disorders fall broadly into 4 categories including:[2]

- Prescribed timing of the sleep-wake schedule or timed physical activity/exercise
- Strategic avoidance or receipt of light
- Use of medications or supplements to shift the sleep-wake cycle or promote alertness
- Somatic interventions to alter bodily functions and impact sleep-wake behaviors

Timed administration of bright light can help to prevent symptoms of excessive sleepiness. A variety of factors can influence efficacy of light exposure including timing and duration of exposure, prior light exposure or “light history”, and light intensity and light wavelength.[2] Sedating drugs (most commonly melatonin) have also been used prior to the desired sleep time to prevent insomnia symptoms. The optimal dose of melatonin has not been determined, and some studies suggest that the timing of melatonin administration may be more important than the dose.[2] In some types of circadian rhythm sleep-wake disorders, stimulants such as modafinil, armodafinil or caffeine have also been used to improve alertness after waking. Drugs that are FDA-approved for circadian rhythm sleep-wake disorders include stimulants (e.g., modafinil, armodafinil) indicated to improve wakefulness in for shift work disorder and tasimelteon indicated for non-24 hour sleep-wake disorder. **Table 2** describes studies evaluated for FDA approval of these drugs**.** Other stimulants and sedating drugs are indicated for related

conditions to improve excessive sleepiness associated with narcolepsy or decrease symptoms of insomnia, but are not specifically FDA-approved for circadian rhythm sleep-wake disorders. Randomized controlled trials (RCTs) have also been completed which evaluate use of stimulants or melatonin receptor agonists in patients with jet lag disorder and irregular sleep-wake rhythm disorder,[12-15] but these agents have not yet been FDA approved for these conditions. In Europe, regulatory approval of modafinil and armodafinil for shift work disorder was withdrawn in 2010 as a result of serious adverse events including neuropsychiatric disorders and fatal skin reactions associated with treatment.[1] European regulatory agencies concluded that benefits of modafinil and armodafinil only outweigh risks when used in patients with narcolepsy.

Historically, insomnia and circadian rhythm sleep-wake disorders have been unfunded on the HERC prioritized list of health services. In 2022, HERC recommended changes to expand non-pharmacological coverage for insomnia and limit duration of drug coverage for insomnia. These changes limit drug coverage of sedative hypnotics to 30 days for treatment of insomnia. In FFS Medicaid, melatonin is covered for people up to 18 years of age, but is not covered for adults due to lack of documented benefit for common sleep disorders like insomnia. Prior authorization is required for all sedatives and stimulants with indications for sleep disorders (e.g., modafinil and armodafinil). These drugs can be covered for unfunded sleep conditions if the sleep disorder is related to a comorbid funded condition and standard treatments for the funded condition were inadequate to control symptoms.

Table 2. Summary of Studies Evaluated for FDA-Approval of Common Circadian Rhythm Sleep-Wake Disorders

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th><th>Notes/Limitations</th></tr>
<tr>
<td>Lockey, et al. 2015.[16]

MC, DB, PC, RCT

Duration: SET: 26 weeks RESET: 11 weeks</td>
<td>SET
1. Tasimelteon 20 mg 1 hour before bedtime (n=42)
2. Placebo (n=42)

RESET: Withdrawal Study
1. Continue tasimelteon 20 mg (n=10)
2. Withdraw to placebo (n=10)</td>
<td>Adults who were blind with non-24H sleep-wake disorder

27 sites in the US and 6 sites in Germany</td>
<td><u>Primary Outcome</u>
Proportion of patients entrained (SET) or who maintain entrainment (RESET)

<u>Relevant Secondary Outcomes Evaluated for FDA approval[10]</u>
Change in total sleep time during the day or night on most symptomatic days/nights</td>
<td>Entrainment
<table><tr><th></th><th>SET</th><th>RESET</th></tr><tr><td>1.</td><td>8/40 (20%)</td><td>9/10 (90%)</td></tr><tr><td>2.</td><td>1/38 (3%)</td><td>2/10 (20%)</td></tr><tr><td></td><td>Difference 17%
95% CI 3.2-31.6;
p=0.0171</td><td>Difference 70%
95% CI 26.4-100;
p=0.0026</td></tr></table>
Change from baseline in sleep time on 25% most symptomatic days/nights (minutes)
<table><tr><th>SET</th><th>Nighttime</th><th>Daytime</th></tr><tr><td>1.</td><td>50</td><td>-49</td></tr><tr><td>2.</td><td>22</td><td>-22</td></tr></table>
<table><tr><th>RESET</th><th>Nighttime</th><th>Daytime</th></tr><tr><td>1.</td><td>-7</td><td>-9</td></tr><tr><td>2.</td><td>-74</td><td>50</td></tr></table></td>
<td>Randomized via interactive voice response system. Baseline characteristics balanced. Blinded with matching placebo. High attrition 24% and 28% in treatment and placebo groups, respectively. Outcomes reported as specified, but a secondary, post-hoc outcome was used for FDA approval. Industry funded.

Ethnicities other than white (81-86%) were underrepresented. Patients with any significant medical or psychiatric disorders were excluded. Of 391 patients evaluated, 136 (35%) were enrolled in the screening period and 84 (62% of enrolled) were randomized.</td>
</tr>
<tr>
<td>Czeisler 2005. [5]</td>
<td>1. Modafinil 200 mg taken 30-60 minutes</td>
<td>Adults with SWD and moderate to</td>
<td><u>Primary</u>
CGI-C (range 1-7)
MSLT</td>
<td>CGI-C at least minimally improved
1. 74%
2. 36%</td>
<td>Randomization method unspecified. Baseline characteristics balanced. Blinded with matching placebo. Per</td>
</tr>
</table>

MC, DB, PC, RCT N=209 Duration: 3 months	before the night shift (n=110) 2. Placebo (n=99)	severe excessive sleepiness during the night shift for at least 3 months, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%) 39 centers in the US between December 2001 and September 2002	<u>Secondary</u> Psychomotor vigilance test KSS (range 1-9)	P<0.001 Change in MSLT from baseline 1. 1.7±0.4 minutes; P<0.001 2. 0.3±0.3 minutes; P=0.24 Psychomotor vigilance test (change from baseline in number of lapses of attention in 20 minutes) 1. -2.6 lapses 2. 3.8 lapses P=0.005 for difference at final visit Change in KSS from baseline 1. -1.5±0.2 2. -0.4±0.2 P<0.001 Patients with accidents or near accidents (reported in patient diary) 1. 46 (29%) 2. 58 (54%) Severe adverse events 1. 6 (5%) 2. 5 (5%)	protocol analysis used with attrition of 25% over 3 months. Industry funded. Of 609 patients screened, 209 (34%) were randomized. Most common reasons for exclusion were failure to meet disease severity markers for polysomnography or sleep latency (n=160, 40%). Average sleep latency was about 2 minutes at baseline. Despite some improvement with modafinil, sleep latency remained below 6 minutes, which indicates excessive sleepiness even with treatment.
Czeisler, et al. 2009.[4] MC, DB, PC, RCT N=254 Duration: 12 weeks	1. Armodafinil 150 mg taken 30-60 minutes before the night shift (n=123) 2. Placebo (n=122)	Night shift workers with moderate-severe SWD, ≥3 months of excessive sleepiness during their shift, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%)	<u>Primary</u> CGI-C (range 1-7) MSLT	CGI-C at least minimally improved 1. 89 (79%) 2. 61 (59%) P=0.001 Change in MSLT from baseline 1. 3.1 minutes (SD 4.5) 2. 0.4 minutes (SD 2.9) Severe Adverse Events 1. 12 (10%) 2. 3 (2%)	Randomization method unspecified. Baseline characteristics balanced Blinded with matching placebo. Assessment of MSLT blinded. Attrition of 31% in placebo and 24% in armodafinil group. Per protocol analysis included only patients with baseline and at least one outcome assessment. Industry funded. Patients were excluded if there was a history of substance abuse, psychiatric disorders, caffeine consumption more than 600mg/day (~6 cups). Of 747 patients screened, 254 (34%) were randomized.

		42 centers in US and Canada from April to December 2004			Severe adverse events were determined by site investigator and included diarrhea, low back pain, and suicidal ideation.

Abbreviations: CGI-C = clinical global impression of change; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; H = hour; KSS = Karolinska Sleepiness Scale, MC = multi-center; MSLT = mean sleep latency test; PC = placebo-controlled; RCT =randomized controlled trial; SWD = shift work disorder; US = United States

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 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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:
Non-24 Hour Disorder
An evidence review was developed by NICE 2021 evaluating use of melatonin for treatment of sleep disorders in adults who are blind.[7] Three studies were identified and included in the review (one RCT and 2 crossover studies).[7] The single RCT did not have adequately reported randomization methods which may increase risk of bias.[7] All studies were small (with the largest enrolling 13 participants) and were likely underpowered to determine differences between groups.[7] All identified studies were of short duration (maximum 12 weeks) with long-term efficacy and safety unknown.[7] Overall, 2 studies (n=20) found no significant improvement in total sleep time with 2 mg or 10 mg of melatonin. One study reported a statistically significant improvement in total sleep time of 0.65 hours (about 40 minutes) with use of melatonin 0.5 mg compared to placebo.[7] Two studies reported melatonin decreased the time spent awake after sleep onset by 0.56 hours with melatonin 0.5 mg and 1.3 hours with melatonin 10 mg.[7] No studies identified a difference with melatonin compared to placebo for sleep latency or quality of life. Overall, authors concluded that evidence is insufficient to determine efficacy and safety for use of melatonin in adults who are blind.[7]

A 2011 Cochrane review evaluated efficacy and safety of melatonin for treatment of sleep disorders in children who are visually impaired.[8] Searches were conducted through July 2011 and failed to identify any RCTs evaluating use of melatonin in this population.[8] Identified literature included non-randomized case series studies, studies in adults who were blind, or studies that included mixed populations where results for the visually impaired cohort could not be independently evaluated.[8] Authors concluded that there was insufficient evidence to support or refute the use of melatonin for sleep disorders in visually impaired children.[8]

Shift Work Disorder - Cochrane

A 2014 Cochrane review evaluated pharmacological interventions for symptoms caused by shift work disorder.[1] Fifteen RCTs were included in the review, and pharmacologic interventions included melatonin (n=9), sedative hypnotics (n=2), modafinil (n=1), armodafinil (n=2), and caffeine combined with pre-shift naps (n=1).[1] Data from these trials was limited by lack of methodological reporting on blinding methods and allocation concealment. Five RCTs had high discontinuation rates (>30%), and there was high risk for selective outcome reporting in multiple trials.[1] When multiple measures were used to evaluate sleepiness or alertness, results for a specific measure were rarely reported when the outcome did not differ from placebo.[1] All included trials were limited by short durations (<7 days) and the long-term efficacy and safety of these treatments for shift work disorder is unclear.

In 7 of the 9 RCTs evaluating melatonin, participants had no reported sleeping problems at enrollment which limits applicability of these results.[1] Doses of melatonin ranged between 1 and 10 mg, and were typically administered after the work shift before going to sleep. Eight trials utilized a cross-over study design, and all RCTs evaluated efficacy of melatonin after one or several consecutive night shifts.[1] Outcomes of total sleep time and sleep onset latency were most commonly reported via patient diaries. There was low quality evidence that melatonin may increase self-reported total sleep time by an average of 24 minutes (95% CI 9.8 to 38.9; 7 RCTs; n=263) during the day after administration and 17 minutes (95% CI 3.71 to 30.22; 3 RCTs; n=234) the night after administration, but did not improve sleep latency or sleep quality compared to placebo.[1] Only one RCT evaluated objective sleep time via actigraphy with no difference in duration of sleep.[1]

RCTs of modafinil and armodafinil enrolled shift workers with SWD and moderate to severe excessive sleepiness (mean sleepiness score of 6 to 6.7 points in the placebo group on the 1 to 9 point KSS scale).[1] Most participants (87-93%) had permanent shift work (vs. rotating shifts). The effect of armodafinil (up to 150 mg) and modafinil (200mg) was evaluated over 3-4 days for outcomes of sleepiness (evaluated via KSS or mean sleep latency test [MSLT]) and alertness (evaluated by reaction time).[1] There was moderate quality evidence that armodafinil and modafinil decreased sleepiness during the night shift evaluating using the KSS scale (MD -0.89, 95% CI -1.37 to -0.4 for armodafinil; MD -0.90, 95% CI -1.45 to -0.35 for modafinil).[1] Serious adverse events were more common with armodafinil than placebo (9.7% vs 2.4%; RR 3.97; 95% CI 1.15 to 13.71). Common adverse events included headache and nausea for both stimulants and insomnia for modafinil. In a long-term extension study of armodafinil, about 11% of patients discontinued treatment due to adverse events.[1] Cardiovascular adverse events and clinically relevant increases in blood pressure were also observed in 6% and 18% of patients prescribed armodafinil, respectively.[1] Serious skin reactions, some of which were fatal, and development of psychiatric disorders including suicidal ideation were also documented in post-marketing studies of modafinil[17] and armodafinil[18] resulting in withdrawal of licensing for the indication of shift work disorder in Europe.[1]

Two small studies (n=88) evaluated the impact of hypnotics (zopiclone and lorazepam) on duration of sleep after a work shift in people with sleeping problems.[1] Outcomes were evaluated after 3 or 7 consecutive days for zopiclone and lorazepam, respectively.[1] There was low quality evidence that zopiclone does not improve total sleep time compared to placebo.[1] Patients prescribed lorazepam may be more likely to have a normal sleep pattern than placebo (89% vs. 64%), but statistical differences were not reported between groups.[1]

A 2010 Cochrane review evaluated caffeine for the prevention of injuries and errors caused by impaired alertness in people with jet lag or shift work disorder.[6] The most common dose administered was 200-400 mg, but doses varied across trials and some trials included weight based dosing.[6] Thirteen RCTs were included, though injuries were not reported as an outcome. Only 2 trials evaluated errors and others assessed cognitive performance using a variety of tests. Data were limited by unclear methods for randomization (6 RCTs), allocation concealment (9 RCTs), inadequate information to assess missing data (11 RCTs), and selective outcome reporting (5 RCTs).[6] Most trials were conducted under simulated conditions limiting applicability to real world settings. Compared to placebo, caffeine improved memory (SMD -1.08; 95% CI -2.07 to -0.09, P = 0.03) and orientation and attention (SMD -0.55; 95% CI -0.83 to -0.27, P0.0001), but did not demonstrate improvement in concept formation and reasoning, verbal functioning and language skills, or perception.[6] Two trials assessed errors with night-time

driving and flight simulation with less errors made if people were administered caffeine compared to placebo. Only one RCT was identified comparing caffeine to each of the following other interventions: naps, bright light, and modafinil.[6] These limited studies did not identify any differences in cognitive performance between treatments.[6] Adverse effects associated with caffeine which were more common than placebo included disruption of subsequent sleep and risk for dependence. Authors conclude that caffeine may improve performance but the degree to which this might reduce injury risk is unknown.[6]

Jet Lag

A 2020 systematic review evaluated pharmacologic and non-pharmacologic treatments for travel fatigue and jet lag in athletes.[3] If the initial literature search failed to identify targeted studies in athletes, then the scope of the search was expanded to healthy populations and evidence was downgraded for applicability. Fourteen RCTs and 8 observational studies evaluated management of jet lag and were included in the review.[3] Eleven studies focused on pharmacological interventions conducted under simulated (n=3) or actual (n=9) travel conditions.[3] Pharmacologic treatments included melatonin (n=2), sedatives (n=1), stimulants (n=4), and melatonin agonists (n=4).[3] There were no studies identified which evaluated travel fatigue. Because of heterogeneous study design, populations, flight direction, outcomes measured and statistical parameters, results were summarized descriptively and a meta-analysis was not conducted. The majority of studies enrolled healthy populations, and only a few studies (n=3) evaluated pharmacologic treatments specifically in athletes.[3] RCTs and observational studies of non-pharmacological interventions had high risk of bias and concerns identified with directness, consistency, precision and publication bias. Most RCTs of pharmacologic interventions were evaluated as having low to moderate risk of bias, and methodologic quality of all observational studies was poor. Major evidence limitations included concerns for consistency, precision, and publication bias.[3]

- There was insufficient evidence for use of melatonin in jet lag symptoms in athletes. Evidence was based on 2 single-arm studies with small sample sizes and no comparator group that had mixed results for management of jet lag.[3]
- There was insufficient evidence for use of sedatives in management of jet lag in athletes. A single observational study was identified that evaluated temazepam for travel symptoms.[3]
- No studies evaluated stimulants or melatonin analogues in athletes. In healthy populations, there was moderate quality evidence from 4 RCTs that stimulants (e.g., armodafinil or caffeine) increased alertness and improve resynchronization of the circadian rhythm.[3]
- There were mixed results for use of melatonin agonists to improve jet lag symptoms following travel in healthy populations. Results from 2 RCTs in tasimelteon showed improved sleep symptoms compared to placebo.[3] There were mixed results in 2 studies of ramelteon for jet lag symptoms. In one study of ramelteon, sleep onset was improved with low doses (1 mg) but not high doses (4-8 mg), alertness was improved with 4mg dose but not low (1 mg) or high (8 mg) doses, and all doses decreased scores on the immediate memory recall test.[3] In the second RCT, there was an observed phase shift in the circadian rhythm with 1-4 mg ramelteon compared to placebo, but no difference in jet lag symptoms.[3]

Authors generally concluded that available evidence for management of jet lag in athletes was of low quality and additional studies were required to draw valid conclusions.

After review, 12 systematic reviews were excluded due to poor methodologic quality (e.g., network meta-analyses),[19-30] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Practice guidelines from the American Academy of Sleep Medicine for the treatment of intrinsic circadian rhythm sleep-wake disorders were updated in 2015.[2] Recommendations were graded as strong or weak recommendations based on degree of clinical certainty regarding net health benefits or harms. For many interventions, there was insufficient evidence to support a recommendation for therapy. There was evidence to support interventions in these populations:

- In adults with advanced sleep-wake phase disorder, evening light therapy is weakly recommended (very low quality evidence).[2]
- In adults, adolescents, and children with delayed sleep-wake phase disorder, strategically timed melatonin or melatonin agonists are weakly recommended (low quality evidence for adults; low-moderate quality evidence for children and adolescents). In children or adolescents, post-awakening light therapy is also weakly recommended (low quality evidence).[2]
- In adults who are blind and have non-24 hour sleep-wake disorder, there is a weak recommendation for strategically timed melatonin or melatonin agonists (low quality evidence).[2]
- In elderly adults with irregular sleep-wake rhythm disorder and dementia, light therapy is weakly recommended (very low quality evidence). There are recommendations against the use of sleep-promoting medications (strong recommendation), melatonin or melatonin agonists (weak recommendation), and combined light therapy and melatonin (weak recommendation) in this population (low to very low quality evidence).[2]
- In children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder, melatonin or melatonin agonists are weakly recommended (moderate quality evidence).[2]

Additional Guidelines for Clinical Context:
Recommendations for extrinsic circadian rhythm sleep-wake disorders were included in practice parameters published by the American Academy of Sleep Medicine in 2007.[31] Because recommendations for intrinsic sleep-wake disorders were updated in 2015,[2] this summary focuses on recommendations for extrinsic disorders (e.g., shift work disorder and jet lag). Recommendations were based on a systematic review of the literature and graded based on evidence. Recommendations were categorized based on certainty of evidence (**Table 3**).[31] This summary will focus on "standard" or "guideline" recommendations.

Table 3. Evidence grades and levels of evidence for Guideline Recommendations[31]

Strength of Recommendation	Degree of Clinical Certainty	Supporting Level of Evidence
Standard	High	High quality RCTs on well-characterized patients or overwhelming evidence from multiple flawed RCTs and/or cohort studies
Guideline	Moderate	Evidence from a cohort study or flawed clinical trial, or consensus from multiple case control studies
Option	Uncertain	Inconclusive or conflicting evidence or conflicting expert opinion. Clinical benefits or risks in this population are uncertain.

Two treatment recommendations were supported by standard recommendations with high quality evidence from well-designed RCTs:
- Planned sleep schedules are recommended in people with shift work disorder.[31] Several lab simulation and observational studies have demonstrated that napping prior to a work night shift will improve alertness, reaction time, and work accidents without affecting post-shift daytime sleep.
- Timed melatonin administration is recommended for people with jet lag disorder.[31] In several studies, melatonin has demonstrated improvements in duration of sleep and sleep quality compared to placebo, with mixed results for improvement of jet lag symptoms. The most effective dose of melatonin is unclear and one study demonstrated decreased efficacy after more than 3 days of use post-travel.

Several treatment recommendations were supported by guideline recommendations with moderate quality evidence from flawed RCTs or observational studies
- Timed light exposure is recommended in people with shift work disorder.[31] In shift work disorder, several studies utilizing a variety of light intensities and durations have demonstrated that administration of bright light for during the work shift demonstrate improvements in timed work performance tasks,

alertness, and mood compared to ordinary light exposure. There is mixed evidence for improvements in daytime sleep in patients with shift work disorder.

- Timed melatonin is recommended in people with shift work disorder.[31] In shift work disorder, several studies have shown that melatonin administered prior to sleep after a work shift improved daytime sleep quality and duration, but failed to improve alertness during the work shift.
- Hypnotics (for insomnia symptoms) or alerting agents like modafinil are recommended in people with shift work disorder.[31] Hypnotics evaluated for shift work disorder included triazolam, temazepam, and zolpicone and generally demonstrated improvements in duration of sleep and sleep quality with inconsistent effects on alertness during the work shift. Authors caution that risks of hypnotics should be weighed against benefits as hypnotics could worsen comorbid conditions. Stimulants like modafinil have shown improved psychomotor performance and alertness during night shifts, but are not a substitute for adequate sleep and have the potential to impair daytime sleep periods.

Randomized Controlled Trials:

A total of 127 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), outcome studied (eg, non-clinical), or inclusion in systematic reviews and guidelines.

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Appendix 1: Preferred Drug List

Sedatives

Generic	Brand	Form	PDL
melatonin	MELATONIN	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 TIME	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	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	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
chloral hydrate	CHLORAL HYDRATE	SYRUP	
dexmedetomidine HCl	IGALMI	FILM	
melatonin/pyridoxine HCl (B6)	MELATONIN-VITAMIN B6	TABLET	

Other Stimulants

Generic	Brand	Form	PDL	Carveout
armodafinil	ARMODAFINIL	TABLET	Y	Y
armodafinil	NUVIGIL	TABLET	Y	Y
modafinil	MODAFINIL	TABLET	Y	Y
modafinil	PROVIGIL	TABLET	Y	Y
solriamfetol HCl	SUNOSI	TABLET	V	Y
pitolisant HCl	WAKIX	TABLET	N	

ADHD Drugs

Generic	Brand	Form	PDL	Carveout
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y	
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y	
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y	
dexmethylphenidate HCl	FOCALIN	TABLET	Y	
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y	
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y	
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y	
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	Y	
methylphenidate	DAYTRANA	PATCH TD24	Y	
methylphenidate	METHYLPHENIDATE	PATCH TD24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y	
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y	
methylphenidate HCl	CONCERTA	TAB ER 24	Y	
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y	
methylphenidate HCl	RITALIN	TABLET	Y	

clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V	Y
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V	Y
guanfacine HCl	INTUNIV	TAB ER 24H	V	Y
viloxazine HCl	QELBREE	CAP ER 24H	V	Y
amphetamine	DYANAVEL XR	SUS BP 24H	N	
amphetamine	DYANAVEL XR	TAB BP 24H	N	
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N	
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N	
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N	
amphetamine sulfate	EVEKEO	TABLET	N	
dextroamphetamine	XELSTRYM	PATCH TD24	N	
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N	
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N	
dextroamphetamine sulfate	ZENZEDI	TABLET	N	
dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N	
methamphetamine HCl	DESOXYN	TABLET	N	
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N	
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N	
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N	
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N	
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N	
methylphenidate HCl	RITALIN LA	CPBP 50-50	N	
methylphenidate HCl	JORNAY PM	CPDR ER SP	N	
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N	
methylphenidate HCl	METHYLPHENIDATE ER	CSBP 40-60	N	
methylphenidate HCl	METHYLIN	SOLUTION	N	
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N	
methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N	
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N	
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N	
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N	
methylphenidate HCl	RELEXXII	TAB ER 24	N	
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N	
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 03, 2023

1	exp "Hypnotics and Sedatives"/	129148
2	exp Melatonin/	22605
3	exp Doxylamine/	397
4	exp Estazolam/	112
5	ramelteon.mp.	493
6	suvorexant.mp.	347
7	exp Triazolam/	1241
8	zaleplon.mp.	437
9	exp Diphenhydramine/	4516
10	exp Doxepin/	847
11	exp Eszopiclone/	134
12	exp Flurazepam/	781
13	exp Midazolam/	9610
14	exp Zolpidem/	1735
15	exp Dexmedetomidine/	5093
16	daridorexant.mp.	47
17	exp Benzodiazepines/	68872
18	exp central nervous system stimulants/ or exp amphetamine/ or exp dexmethylphenidate hydrochloride/ or exp dextroamphetamine/ or exp methylphenidate/ or exp modafinil/	101793
19	exp Atomoxetine Hydrochloride/	1337
20	exp Clonidine/	13470

21	exp Guanfacine/	751
22	exp Viloxazine/	242
23	serdexmethylphenidate.mp.	5
24	armodafinil.mp.	225
25	solriamfetol.mp.	83
26	pitolisant.mp.	171
27	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	289392
28	exp Sleep Disorders, Circadian Rhythm/	2685
29	delayed sleep-wake phase disorder.mp.	88
30	advanced sleep-wake phase disorder.mp.	11
31	irregular sleep-wake rhythm disorder.mp.	18
32	non-24 hour sleep-wake rhythm disorder.mp.	18
33	shift work disorder.mp.	153
34	exp Jet Lag Syndrome/	584
35	28 or 29 or 30 or 31 or 32 or 33 or 34	2805
36	27 and 35	632
37	limit 36 to (english language and humans)	537
38	limit 37 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 equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	127

Appendix 3: Key Inclusion Criteria

Population	Circadian Rhythm Sleep Disorders (e.g., delayed or advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24 hour sleep-wake rhythm disorder, shift work disorder, jet lag) in adults and children.
Intervention	Stimulants (**Appendix 1**) Sedatives (**Appendix 1**)
Comparator	Active medication comparators listed in **Appendix 1** or placebo
Outcomes	Symptoms (e.g., excessive daytime sleepiness, amount and quality of sleep) Quality of life Function (e.g., impacts on driving, work, school)
Setting	Outpatient

Appendix 4: Proposed Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Long-term treatment of insomnia with sedatives is not funded.
- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) 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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

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 request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. 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 #5	**No:** Go to #5
5. 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 ~~lifetime~~5 years	**No:** Go to #6

Approval Criteria		
6. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch.	**No:** Go to #8
8. 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.
9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10	**No:** Go to #11

Approval Criteria		
10. Is the patient on CPAP?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
11. Is the request for treatment of insomnia?	**Yes:** Go to #12	**No:** Go to #13
12. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment (CBT-I), failed to have benefit in symptoms after 5-6 CBT interventions, OR have inability to access CBT-I?	**First request:** Sedative treatment can be approved for 30 days. Long-term treatment must document that benefits outweigh risks. **Subsequent request:** Go to **Renewal Criteria**	**No:** Pass to RPh. Deny; medical appropriateness.
13. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Yes:** Document supporting literature and approve 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** For current age ≥ 21 years: Deny; not funded by OHP. For current age < 21 years: Go to #14
14. 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 #15 Document baseline severity	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
15. 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 for treatment of an unfunded condition previously approved by FFS?	**Yes:** Go to #3	**No:** Go to #4
3. Is there documentation of improvement (e.g., of symptoms, function, quality of life, etc) since treatment was started?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Is there documentation based on medical records that the patient and provider have discussed whether benefits of ongoing ~~benefits~~ 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:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness.

Sleep-Wake Medications

Goal(s):

- To promote safe use of drugs for obstructive sleep apnea and narcolepsy.
- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit

Requires PA:

- Modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea
- Solriamfetol
- Pitolisant

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. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)
• Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	Not FDA approved; insufficient evidence

• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil	18 years	250 mg
Modafinil	18 years	200 mg
Solriamfetol	18 years	150 mg
Pitolisant	18 years	17.8 mg (poor CYP2D6 metabolizers)

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA-approved for narcolepsy in this age group.
3. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #~~5~~6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) despite lifestyle modifications (e.g., strategic bright light receipt or avoidance, sleep hygiene, dietary changes, etc)?	**Yes:** Document symptom severity. Go to #6 Evidence supports modafinil and armodafinil in moderate-severe shift work disorder (e.g., sleep latency ≤ 6 minutes) and risks likely outweigh benefits in patients with mild symptoms.	**No:** Pass to RPh. Deny; medical necessity.
~~5.~~6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #7~~6~~	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~6.~~7. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #8~~7~~
~~7.~~8. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #9~~8~~	**No:** Go to #10~~9~~
~~8.~~9. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #10~~9~~ Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
~~9.~~10. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #11~~0~~ Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
~~10.~~11. Is the request for solriamfetol or pitolisant?	**Yes:** Go to #12~~1~~	**No:** Go to #16~~5~~
~~11.~~12. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13~~2~~
~~12.~~13. Is the request for solriamfetol?	**Yes:** Go to #14~~3~~	**No:** Go to #16~~5~~
~~13.~~14. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15~~4~~

Approval Criteria		
~~14.~~15. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #19~~8~~ Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
~~15.~~16. Is the patient of childbearing potential?	**Yes:** Go to #16	**No:** Go to #19~~8~~
~~16.~~17. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #18~~7~~
~~17.~~18. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #19~~8~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~18.~~19. Is the request for treatment of narcolepsy for a drug FDA-approved for the condition (Table 1)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #20~~19~~
~~19.~~20. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) for a drug FDA-approved for the condition (see Table 1)?	**Yes:** Go to #21~~0~~	**No:** Go to #22~~1~~
~~20.~~21. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness

Approval Criteria		
~~21.~~22. Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #23~~2~~
~~22.~~23. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #24~~3~~
23. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for “medical appropriateness”. • Evidence to support cognition enhancement is insufficient and should be denied for “medical appropriateness”. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Renewal Criteria		
1. Is the request for solriamfetol?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5
4. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit. For Epworth Sleepiness Scale, and improvement of at least 3 points is considered clinically significant.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: 10/1/2020 (DE); 2/2020; 7/19; 03/16; 09/15
Implementation: 11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16

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Drug Class Update with New Drug Evaluation: Amyotrophic lateral sclerosis

Date of Review: April 2023

Date of Last Review: Class N/A; Edaravone Injection July 2018
Dates of Literature Search: 04/30/2018-11/10/2022 Edaravone
01/01/2012-11/10/2022 ALS class
No start to 01/18/23 RELYVRIO

Generic Name: sodium phenylbutyrate and taurursodiol

Brand Name (Manufacturer): RELYVRIO (Amylyx Pharmaceuticals)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To review new evidence for efficacy and harms of the combination product, sodium phenylbutyrate and taurursodiol, in the treatment of amyotrophic lateral sclerosis (ALS). This review will also evaluate the evidence for other agents approved to treat ALS and update prior authorization criteria as needed.

Plain Language Summary:
- This review looks at new evidence for medicines that are used for amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.
- Amyotrophic lateral sclerosis is a condition that makes a person's muscles weaker, until it becomes difficult to walk and breathe. People with amyotrophic lateral sclerosis usually live for about 2 to 5 years once diagnosed with this condition.
- Three medicines are Food and Drug Administration approved to treat amyotrophic lateral sclerosis. These are riluzole, edaravone, and the new medication sodium phenylbutyrate-taurursodiol. Riluzole is the oldest medicine and evidence shows it may help a person live 2-3 months longer.
- A recent summary of older evidence shows that edaravone may help to slow down how quickly amyotrophic lateral sclerosis makes a person sick.
- A new medicine, sodium phenylbutyrate-taurursodiol (RELYVRIO), has been approved by the Food and Drug Administration to treat amyotrophic lateral sclerosis. Evidence shows it may slow down how quickly amyotrophic lateral sclerosis makes a person sick.
- The Drug Use Research and Management group recommends riluzole be available for use.
- The Drug Use Research and Management group recommends providers explain why someone needs edaravone and sodium phenylbutyrate-taurursodiol before Medicaid will pay for it. This process is called prior authorization.

Author: Sara Fletcher, PharmD, MPH, BCPS

Research Questions:

1. What is the efficacy of sodium phenylbutyrate-taurursodiol compared to placebo or currently available treatments for amyotrophic lateral sclerosis (ALS)?
2. What is the safety of sodium phenylbutyrate-taurursodiol for treatment of ALS?
3. What is the comparative efficacy and safety of agents approved for ALS?
4. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a specific agent for ALS?

Conclusions:

- This update includes information from one high-quality systematic review[1] and one randomized control trial.[2]
- There is low-quality evidence from a Canadian Agency for Drugs and Technologies in Health (CADTH) review that edaravone reduces the change in ALS Functional Rating Scale-Revised (ALSFRS-R) over 6 months. A CADTH common drug review[1] of 3 randomized controlled trials (RCTs) and 1 extension study of edaravone found no evidence that showed a reduction in mortality or improvement of the survival study of death, disability of independent ambulation, loss of upper-limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech. Only one RCT (Study 19) showed a statistically significant reduction in the change in ALSFRS-R slope over 6 months (between group least squares [LS] mean difference 0.47, 95% confidence interval [CI] 0.19 to 0.74; p=0.001).[1]
- Edaravone is available in a new, oral suspension formulation.[3]
- There is low-quality evidence from one fair-quality phase II trial that sodium phenylbutyrate-taurursodiol reduced the rate (slope) of decline in the total score on the ALSFRS-R from baseline to week 24 compared to placebo (sodium phenylbutyrate-taurursodiol -1.24 points/month vs. placebo -1.66 points/month; difference 0.42 points/month; 95% CI 0.03 to 0.81; p=0.03) in patients with definite ALS.[2] A minimum clinically important difference (MCID) is not established for this endpoint, though experts have stated a difference of at least 2 points over a 6 month period for most patients would be considered clinically meaningful if reproduced in multiple studies.[1] Trial is downgraded for attrition bias. Additionally, there are concerns related to statistical assumptions with handling of missing data in light of functional status primary endpoint which does not account for mortality.[2]
- There is insufficient long-term evidence on safety of sodium phenylbutyrate-taurursodiol. Rates of serious adverse events were similar when compared with placebo (12% vs. 19%) at 24 weeks. There were 5 deaths in sodium phenylbutyrate-taurursodiol group and 2 in the placebo group (2:1 randomization).[2]
- There is insufficient direct comparative evidence for agents in this class.
- Previous evidence has shown riluzole may prolong survival by 2-3 months.[4]
- Evidence for edaravone is primarily limited to a Japanese population[1] and evidence for riluzole is primarily from a White population.[2] There is insufficient evidence on efficacy or harms data for other subgroups.

Recommendations:

- Designate riluzole as preferred on the preferred-drug list (PDL).
- Designate edaravone and sodium phenylbutyrate-taurursodiol as non-preferred on the PDL.
- Implement prior authorization (PA) criteria for sodium phenylbutyrate-taurursodiol and update edaravone PA criteria as proposed **(Appendix 5)**
- Review costs in executive session

Summary of Prior Reviews and Current Policy

- A new drug evaluation (NDE) for edaravone injection was presented to the Pharmacy and Therapeutics (P & T) committee in July 2018. The NDE of edaravone evaluated Study 19 in detail.[5] The NDE found:
  - There is insufficient evidence to determine if edaravone has any significant impact on functional status or disease progression in all ALS patients beyond 6 months.
  - There is insufficient evidence to evaluate the long-term safety of edaravone.
  - There is insufficient evidence to compare edaravone to any other ALS therapies or in specific subpopulations other than Japanese patients.
- Both edaravone formulations (oral and injection) are subject to PA criteria and require concurrent use of riluzole if no contraindication or intolerance.
- Neither riluzole nor edaravone have a status designated on the PDL.

Background:

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's or Charcot's disease, is the most common degenerative and fatal motor neuron disease.[6] There is increased awareness that frontal and temporal lobes are involved, in addition to motor neurons, in a subset of patients.[7] The incidence is roughly 1-2 per 100,000 and prevalence of 10-12 per 100,000 in the United States (US) and Europe.[8] Men are usually twice as commonly affected as women.[8] ALS symptoms typically do not develop until 50 years of age, and the disease is usually diagnosed between 55 and 65 years of age. Although there is variation in ALS presentation and progression, the average life expectancy is two to five years from the time of diagnosis.[9] Only about 10-15% of ALS patients live more than 10 years from disease onset, and 50% survive 30 months from symptom onset.[8] Diagnosis is made using medical history, physical examination, electrodiagnostic testing, and neuroimaging studies to rule out of other neurological conditions such as myasthenia gravis or adult onset spinal muscular atrophy.[8] The revised El Escorial criteria are used most often, though more commonly in clinical trials than clinical practice.[8] The El Escorial criteria is a diagnostic scale based on locations of motor neuron dysfunction rather than a severity rating. ALS is classified as clinically definite, probable, laboratory-supported probable, possible, and suspected.[8] Other classification systems including Awaji criteria, which has low test-retest reliability, or the simplified 2019 Gold Coast Criteria, which awaits validation.[8] Genetic testing may be used in those with family history. Early stages of ALS are marked by muscle stiffness, asymmetric limb weakness, cramping and fatigue.[10] Twenty percent of ALS patients exhibit bulbar symptoms such as slurred speech and dysphagia.[11] As ALS progresses, selective degeneration of upper and lower motor neurons eventually results in loss of coordination and muscle strength leading to complete paralysis, respiratory failure, and death.[11] Up to 30% of ALS patients may experience significant cognitive or psychological impairment as well as depression and mood imbalance.[12] Subtypes of ALS are progressive bulbar palsy, limb-onset ALS, progressive muscular atrophy, and upper motor neuron predominant ALS.[7] Cognitive impairment may be present in 45% of patients with ALS.[7] ALS diagnosis allows Medicare coverage for disability without a 24-month waiting period.[13] Based on claims data, Oregon Medicaid has over 100 identified cases of ALS, with about 20% of them in the Fee-for-Service (FFS) program. Roughly two-thirds of persons with ALS are Medicare dual enrolled, and approximately half of dual enrolled members are age 65 years or older.

The etiology of ALS is largely unknown, however, mitochondrial abnormalities, signs of oxidative stress, and elevated 3-nitrotyrosine and protein carbonyl levels have been observed in many patients diagnosed with ALS.[6,14] Established risk factors for development of ALS are age and family history. Sporadic ALS generally affects individuals in their late 50s to early 60s. Only 10-15% of ALS cases are familial ALS, also called genetic[8], and typically emerge a decade earlier in patients aged in their 40's and 50's.[9,14] There are no clinical laboratory tests that confirm diagnosis of nongenetically determined ALS.[10]

There is no cure for ALS and effective management is primarily focused on symptomatic and supportive care for the patient's physical, emotional and psychological needs.[15] Therapy outcomes which are of clinical value to ALS patients include mobility, muscle strength, quality of life, disease progression, and

mortality. A variety of tools and clinical measures have been employed to manage and monitor ALS patients at various stages of functional decline.[15,16] Guidelines from the American Academy of Neurology (AAN) recommend noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) as important but underutilized treatments for ALS patients.[15] Noninvasive ventilation may be useful at earlier stages of ALS for the treatment of respiratory insufficiency in order to lengthen survival, slow forced vital capacity decline, and improve patient quality of life.[17] Spirometry with forced vital capacity (FVC) has been commonly used to diagnose diaphragmatic weakness and symptom progression in ALS patients.[8,17] Slow vital capacity (SVC) is the maximal amount of air exhaled in a relaxed expiration. Testing of FVC is recommended every 3-6 months, FVC < 50% may indicate imminent respiratory failure.[18] Respiratory system dysfunction is often the terminal event for ALS patients. Tracheostomy placement ranges from 2% to 15% and varies by country.[18] Due to the loss of motor function, the majority of patients will eventually require assistance with activities of daily living (ADL).[17] Surgically placed feeding tubes (e.g. PEG tubes) have been used for nutrition to help stabilize patient weight and prolong survival.[15]

The ALSFRS-R is a tool widely used by clinicians to assess disease progression in ALS patients.[19] There are 12 items in 4 subdomains of bodily function including bulbar, fine motor, gross motor, and breathing.[2] Each is scored from 0, indicating total loss of function to 4, indicating no loss of function.[2] The ALSFRS-R enables clinicians to score the patient's physical function on a scale from 0 (worst) to 48 (normal).[19] The ALSFRS-R has been considered by some to be an improvement over the original ALSFRS due to its incorporation of 3 additional questions regarding dyspnea, orthopnea, and the need for respiratory support.[19,20] Some studies have used changes in the ALSFRS-R to make survival predictions.[21] However, there has been criticism regarding use of the ALSFRS-R scale because it may not be sensitive to heterogeneity in ALS disease progression especially among multiple domains over short time periods.[16,19] An additional validity concern of the ALSFRS-R is its reduced sensitivity for detection of change in low-functioning ALS patients as well as the potential for scores to be affected by mood or effort.[16,22] The MCID on the ALSFRS-R score is unclear,[22] although clinical experts with CADTH have stated a difference of at least 2 points over a 6 month period for most patients would be considered clinically meaningful if reproduced in multiple studies.[1] Changes in the ALSFRS-R have been correlated with patient-perceived changes of physical, emotional, and social function, but patients may be unable to perceive an intervention effect until its impact on the ALSFRS-R is 9 points or more.[23] Clinical trials have shown that the ALSFRS-R declines at a rate of -0.92 units per month in ALS patients.[24] Surveys of clinicians estimate that an ALSFRS-R slope change (score vs. time) by 20-25% or more would be considered clinically meaningful.[24]

Pharmacological treatment options to slow disease progression are few, and there is no evidence that familial ALS or sporadic ALS patients respond better to any particular available therapy.[25] Gamma aminobutyric acid (GABA) modulators and recombinant human insulin-like growth factor-1 (IGF-1) have been studied to assess improved function or survival in adult ALS patients, but there is insufficient evidence available to support use of either agent to mitigate the degenerative effects of the disease.[25-27] Riluzole (1995)[28] and edaravone (injection 2017, oral suspension 2022)[3] are currently available FDA approved products to manage ALS. The AAN and National Institute for Heath and Care Excellence (NICE) guidelines both recommend that riluzole be offered to ALS patients by a neurological specialist to slow disease progression.[15,29] A 2011 updated Cochrane Review examined the efficacy of riluzole in prolonging survival and in delaying the use of surrogates to sustain survival.[30] Evidence from 4 RCTs of acceptable methodological quality with 1477 ALS patients were reviewed.[30] Three of the 4 studies with full data on tracheostomy-free survival were compared.[30] Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials (hazard ratio (HR) 0.80, 95%, CI 0.64 to 0.99, P= 0.042).[30] The third trial included older patients with more advanced disease, however, the pooled treatment effects were still significant (HR 0.84, 95% CI 0.698 to 0.997, P= 0.046).[30] The results indicated that riluzole therapy for ALS patients was associated with an increased median survival benefit from 11.8 to 14.8 months versus placebo, and the author's concluded riluzole 100 mg was reasonably safe and probably prolongs survival by 2 to 3 months in patients with ALS.[30] The exact mechanism for the therapeutic benefit of riluzole in ALS has not been determined. Assessment of functional improvement with the ALSFRS-R tool was not performed in riluzole-treated patients.[30] Since last review, additional data regarding long-term safety and efficacy of edaravone have been published, though open-label design and post-hoc analyses introduce bias to the results.[31,32]

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 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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:
Edaravone Clinical Review Report (CADTH)
A CADTH common drug review of edaravone (RADICAVA, 30 mg/100 mL infusion bag) for use in ALS was published in April 2019.[1] Four RCTS were included: Study 16, Study 18, Study 19 (detailed in previous NDE[5] from July 2018), and Study 17, which was a parallel-group extension trial of Study 16.[1] All studies were conducted in Japan and were phase III. Enrollment varied in these placebo-controlled trials with Study 16 (n=206) and 17 (n= 206 randomized; n=181 participated) larger than Study 19 (n=137) and Study 18 (n=25).[1] All RCTs included definite or probable ALS cases with varying baseline FVC requirements of greater than 60, 70, or 80%.[1] Primary end point was change in ALSFRS-R for all trials, with other endpoints including time to death or disease progression (e.g. tracheostomy) and additional function and safety endpoints.[1] Concomitant riluzole use was approximately 85-90% for most treatment groups.[1] There were imbalances in study discontinuations between groups and some notable differences in baseline characteristics such as patients with probable versus definite ALS.[1]

Table 1. Key efficacy and safety results[1]

Outcomes	Study 16		Study 17		Study 18		Study 19	
	PL N=104	ED N=101	ED-PL N=44	ED-ED N=48	PL N=12	ED N=13	PL N=68	ED N=69
Survival analysis for disease progression* Total N (%)	37 (35.6)	38 (37.6)	13 (29.5)	19 (39.6)	4 (33.3)	7 (53.8)	6 (8.8)	2 (2.9)
Death	2 (1.9)	2 (2.0)	1 (2.3)	1 (2.1)	0	1 (7.7)	0	0
P value for log-rank test	0.3814		0.1540		0.1058		0.1284	
P value for generalized Wilcoxon test	0.3992		0.0684		0.0782		0.1415	
ALSFRS-R	PL N=99	ED N=100	ED-PL N=41	ED-ED N=45	PL N=12	ED N=13	PL N=66	ED N=68

Change/month from baseline slope LS mean (SE)	-1.05 (0.16)	-0.99 (0.16)	-1.62 (0.29)	-0.97 (0.28)		-0.96 (0.3)	-1.14 (0.29)	-1.35 (0.12)	-0.88 (0.12)
Between group difference LS mean (95% CI)	0.06 (-0.24 to 0.37)		0.66 (-0.09 to 1.41)			-0.18 (-1.02 to 0.66)		**0.47 (0.19 to 0.74)**	
P value	0.6785		0.0858			0.6614		**0.001**	
Safety	PL N=104	ED N=102	ED-PL N=45	ED-ED N=48	PL-ED N=88	PL N=12	ED N=13	PL N=68	ED N=69
Subjects with > 0 SAEs N (%)	24 (23.1)	18 (17.6)	13 (28.9)	25 (52.1)	39 (44.3)	2 (16.7)	3 (23.1)	16 (23.5)	11 (15.9)
Deaths, N (%)	2 (1.9)	3 (2.9)	1 (2.2)	4 (8.3)	1 (1.1)	0	1 (7.7)	0	0
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CI = confidence interval; ED = edaravone; LS = least squares; N = number; PL = placebo; SAEs = serious adverse effects; SE = standard error *Death, disability of independent ambulation, loss of upper-limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech									

Only study 19 demonstrated a statistically significant response in rate of ALSFRS-R decline change from baseline (LS mean difference 0.47; 95% CI 0.19 to 0.74) and differences in survival, respiratory function, and quality of life are not clear.[1] Statistically significant differences were not seen in the other studies. Given the overall natural history of ALS, edaravone should be considered in the majority of ALS patients with preserved respiratory function and functional independence per the authors.[1]

After review, 16 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical, non-FDA approved indication), previously included in 2018 DURM review,[4] or CADTH reviews only detailing CENTAUR trial which is evaluated below.[33,34]

New Guidelines:
None

After review, 1 guideline[35] was excluded due to topic focus (not ALS, non-FDA approved indications).

New Formulations or Indications:
Edaravone (RADICAVA ORS) oral suspension was approved in May 2022 based on pharmacokinetic comparison with an equivalent area under the curve (AUC) and maximum concentration (Cmax) not less than the intravenous infusion at the approved dose.[3] It should be used orally or via feeding tube, in the morning after overnight fast and without food consumption for 1 hour after administration due to significant reduction in AUC and Cmax when given with a high-fat meal.[3] The daily recommended dose is 105 mg (5mL) and the administration interval mirrors that of RADICAVA intravenous injection with an initial treatment cycle of daily for 14 days, followed by a 14 day drug free period. Subsequent cycles include daily dosing in 10 out of 14 days with a 14 day drug free period.[3] Patients may change from intravenous to oral and continue same dosing schedule.[3]

New FDA Safety Alerts:
None

Randomized Controlled Trials:
A total of 81 citations were manually reviewed from the initial literature search. After further review, 81 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).

NEW DRUG EVALUATION:

See **Appendix 4** 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.

Sodium Phenylbutyrate-taurursodiol (RELYVRIO, previously AMX0035)[36] was approved in September 2022 by the FDA for the treatment of ALS in adults.[37] Taurursodiol is also known as tauroursdeoxycholic acid[37] and the drug combination is known in Canada as sodium phenylbutyrate and ursodoxicoltaurine (ALBRIOZA).[33,34,36] Each of the component agents has other therapeutic uses as monotherapy. Sodium phenylbutyrate (BUPHENYL) has FDA approval for treatment of urea cycle disorders, as does the prodrug glycerol phenylbutyrate (RAVICTI).[38] Taurursodiol is approved in Italy, China, and Turkey for treatment of bile production disorders, while its metabolite, ursodiol (UDCA) is FDA approved for treatment of primary biliary cirrhosis.[38]

Clinical Efficacy:
FDA approval was based on CENTAUR (NCT03127514) a phase II, multicenter, double-blind, placebo-controlled, parallel-group RCT evaluating sodium phenylbutyrate 3 g with taurursodiol 1 g administered orally or via feeding tube once daily for 3 weeks, then twice daily, versus placebo over 24 weeks in patients with a diagnosis of definite ALS using the revised El Escorial criteria and SVC exceeding 60% of predicted for age, sex, and height.[2,39] Riluzole use was allowed if dosing remained stable for a minimum of 30 days before screening.[2] The protocol was amended in 2017 following FDA approval of edaravone to allow its use before or during the study.[2,39] An open-label extension study (NCT03488524) to evaluate long-term safety up to 132 weeks has also been completed, results have been reported for secondary efficacy outcomes.[40-42] More details on study design and risk of bias are included in **Table 4**.

The study groups were primarily male (69%) and White (95%) with an average age of 57.5 years (n=137).[2] Baseline score and slope of ALSFRS-R were similar between groups after a 2:1 randomization scheme, though use of concomitant ALS treatments was lower for the sodium phenylbutyrate-taurursodiol group than placebo for riluzole (68% vs. 77%), edaravone (25% vs. 50%) and both (22% vs. 40%).[2] Bulbar onset of disease was more common with sodium phenylbutyrate-taurursodiol (30%) compared to placebo (21%).[2]

The primary endpoint was the rate (slope) of decline in the total score on the ALSFRS-R from baseline to week 24.[2] The sodium phenylbutyrate-taurursodiol group had a -1.24 points/month change compared to -1.66 points/month with placebo (difference 0.42 points/month; 95% CI 0.03 to 0.81; p=0.03).[2] This calculation relies on an assumption of linearity in ALSFRS-R over time. When using a Mean-By-Visit model which does not rely on linearity the FDA did not find a statistically significant treatment difference (estimated difference 1.86, standard error 1.04; p=0.0749).[38] Attrition from drug discontinuation due to adverse events was higher with sodium phenylbutyrate-taurursodiol (19%) versus placebo (8%) and fewer people taking sodium phenylbutyrate-taurursodiol completed the trial drug regimen compared with placebo (69% vs. 77%). Completion of 24-week follow-up was similar between groups (sodium phenylbutyrate-

taurursodiol 77% vs placebo 79%). The primary endpoint was calculated using a modified intention to treat (mITT) population which excluded 2 patients who died after randomization and receiving active drug treatment, but who did not have a post-baseline ALSFRS-R score. The analysis uses unverifiable missing data assumptions and may be confounded by patient deaths.[38] The primary endpoint is a measure of functional status alone and the risk for attrition bias is high. A post-hoc joint rank assessment (ranking subjects first by time to death then change from baseline in ALSFRS-R) was performed by the study (rank estimate sodium phenylbutyrate-taurursodiol 72.93 vs. rank estimate placebo 59.07, difference 13.85; p=0.0381). This analysis incorrectly used "last observation carried forward" to account for missing data in a chronic, deteriorating condition. FDA analysis of the joint-rank assessment using multiple-imputation based on a missing at random assumption found no statistical difference in the mITT population (p=0.063) or the ITT population (p=0.079).[38] The secondary efficacy outcomes had a hierarchal analysis order and failed to reach statistical significance on the first level, therefore all remaining secondary efficacy analyses (including survival) are considered exploratory.[2,38]

Risk of bias was generally low other than significant concerns related to attrition and missing data modeling in statistical analysis described above. Racial homogeneity of study population limits applicability to Medicaid population. Concomitant use of existing medications for ALS was low and riluzole use (68-77%) was somewhat lower than in studies with edaravone (~85-90%).[1] Additional research with larger study populations and longer duration with primary survival endpoints in addition to functional outcomes are needed to understand true place in therapy. A phase III study (NCT05021536) with 600 participants is anticipated to conclude in late 2023.[43]

Clinical Safety:
Serious adverse events occurred in 12% of patients in the sodium phenylbutyrate-taurursodiol group and 19% of patients in the placebo group; all discontinuations due to serious adverse events were considered unrelated to the intervention in both groups (1% vs. 6%).[2] Discontinuation due to any adverse event were higher for the sodium phenylbutyrate-taurursodiol group (19% total, 15% considered due to intervention) than the placebo group (8% total, 2% considered due to intervention).[2] There were 7 deaths overall, 5 in the intervention group (including the 2 deaths excluded during the mITT analysis) and 2 in the placebo group.[2]

The most common adverse reactions which occurred more frequently in the sodium phenylbutyrate-taurursodiol group than the placebo group were gastrointestinal disorders (67% vs. 60%); respiratory, thoracic, and mediastinal disorders (33% vs. 21%); skin and subcutaneous-tissue disorders (18% vs. 17%); metabolism and nutrition disorders (11% vs 8%); cardiac disorders (8% vs. 0%); and eye disorders (6% vs. 2%).[2] Individual adverse reactions reported more often in phenylbutyrate-taurursodiol treated patients and at least 5% in both groups are in **Table 2**.

Table 2. Adverse Reactions[37]

Adverse Reaction	Sodium phenylbutyrate-taurursodiol N=89 %	Placebo N=48 %
Diarrhea	25	19
Abdominal pain	21	13
Nausea	18	13
Upper Respiratory tract infection	18	10
Fatigue	12	6

Salivary hypersecretion	11	2
Dizziness	10	4

There are no listed contraindications for sodium phenylbutyrate-taurursodiol.[37] There are warnings and precautions against use in patients with enterohepatic circulation disorders, pancreatic disorders, or intestinal disorders because taurursodiol is a bile acid.[37] There may be increased risk for diarrhea, as well as altered pharmacokinetics in these patients, so they were excluded from studies.[37] There is an additional warning and precaution in patients sensitive to high sodium intake such as people with heart failure, renal impairment, or hypertension.[37] Each packet contains 464 mg sodium which would provide 938 mg/day in patients on twice daily maintenance dosing.[37]

The matching placebo included a number of excipients, including anhydrous sodium phosphate dibasic and sorbitol.[39] It is unclear what the total sodium content of placebo would be, or if other excipients contributed to the very high rate of gastrointestinal disorder adverse events seen in the placebo group (60%).[2]

Look-alike / Sound-alike Error Risk Potential: Ursodiol (ACTIGALL), sodium phenylbutyrate (BUPHENYL), glycerol phenylbutyrate (RAVICTI)

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Survival
2) Ventilator/tracheostomy free survival
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) ALSFRS-R score (functional status) over 6 months

Table 3. Pharmacology and Pharmacokinetic Properties.[37]

Parameter	
Mechanism of Action	Unknown
Oral Bioavailability	Sodium phenylbutyrate: Tmax = 0.5 hour; High fat meal reduced Cmax (76%) and AUC (54%) Taurursodiol: Tmax = 4.5 hours, high fat meal did not affect Cmax, increased AUC (39%)
Protein Binding	Sodium phenylbutyrate: 82% Taurursodiol: 98%
Elimination	Sodium phenylbutyrate (~80-100%) excreted in urine within as conjugated phenylacetylglutamine.
Half-Life	Not reported
Metabolism	Phenylactate is major metabolite of phenylbutyrate; ursodiol and glycol-ursodiol are major metabolites of Taurursodiol.

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; Tmax = time to maximum concentration.

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Paganoni S, et al.[2,38,39,44] CENTAUR Phase II, RCT, DB, PC	1. sodium phenylbutyrate 3g-taurursodiol 1g 2. placebo (includes multiple excipients) Given once daily for 3 weeks, then twice daily (morning and evening) through week 24 if tolerated. Dissolved in room temperature water and given orally or via feeding tube 2:1 randomization OL extension continued for up to 132 weeks.	Demographics: -Male sex 1. 61 (70%) 2. 32 (67%) -White 1. 82 (94%) 2. 46 (96%) -Bulbar onset 1. 26 (30%) 2. 10 (21%) -Riluzole use 1. 59 (68%) 2. 37 (77%) -Edaravone use 1. 22 (25%) 2. 24 (50%) -Both Riluzole & Edaravone use 1. 19 (22%) 2. 19 (50%) -ALSFRS-R score 1. 35.7 ± 5.8 2. 36.7 ± 5.1 Key Inclusion Criteria: - 18-80 years -ALS by revised El Escorial criteria within 18 mo of onset -SVC > 60% predicted for age, height, and gender -no use of riluzole OR riluzole dose stable for 30 days pre-screening Note: edaravone FDA approved while CENTAUR study	mITT: 1. 87 2. 48 Attrition: 1. 31% 2. 23% Did not complete trial regimen 1. 23% 2. 21% Did not complete 24-week follow up	Primary Endpoint: Rate (slope) of decline in total ALSFRS-R from baseline to week 24 1. -1.24 pts/mo 2. -1.66 pts/mo Difference 0.42 pts/month 95% CI 0.03 to 0.81 P=0.03	n/a	Death: 1. 5 (6%) 2. 2 (4%) Serious ADR: 1. 12% 2. 19% Discontinuation due to ADE: 1. 17 (19%) 2. 4 (8%)	n/a	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Computer generated permutated block randomization, no stratification. Error in kit distribution gave first 17 participants active drug, and next 9 placebo. Sensitivity analysis excluding these participants yielded similar results to prespecified primary analysis. Performance Bias: (Low) Double-blind with placebo matched to taste, appearance, and dissolution profile. Detection Bias: (Low) ALSFRS-R test given via phone. All ALSFRS-R, VC, and ATLIS evaluators NEALS certified. Blinding maintained throughout trial period. Independent DSMB received blinded and unblinded summary reports. Attrition Bias: (High) High overall attrition, mITT for those who discontinued drug but remained in trial and excluding 2 deaths where patients were randomized to treatment arm and received drug but had no post-baseline ALSFRS-R measurements (first assessment scheduled 21 ± 5 days post-baseline visit). Joint rank analysis primary endpoint (incorporating functional status and mortality) would have been more appropriate per FDA. No imputation performed for missing data, though a sensitivity analysis performed to evaluate effects of missing data. FDA review notes possible confounding of functional endpoints by loss of data due to patient deaths, and that analysis relies on unverifiable missing data assumptions. Reporting Bias: (Low) Protocol published Other Bias: (Unclear) Designed and conducted through NEALS network; collaboration with manufacturer for trial design, data analysis, and manuscript development with confidentiality agreements with authors. FDA statistical review found impact from more influential individual test sites affected overall

		ongoing, protocol amended to allow edaravone at time of screening or to start while enrolled in study Key Exclusion Criteria: -presence of tracheostomy -abnormal liver function defined as AST and/or ALT >3x ULN -poorly controlled arterial hypertension (SBP>160 mmHg or DBP>100 mmHg) -history of cholecystectomy -Biliary disease which impedes biliary flow						statistical significance of treatment difference. Additionally, the primary analysis result uses a slope analysis that assumes linearity of ALSFRS-R over time, which is not established. **Applicability**: Patient: Study population primarily White and less representative of disease and Medicaid population as a whole. Intervention: Dose appropriate for Phase II trial based on pilot studies. Comparator: Placebo appropriate given few treatment options. Therapy with concomitant riluzole (if no contraindication) would be useful as that is current standard of care. Outcomes: Functional outcome measure used for short term setting. Information related to clinical outcomes (mortality, QoL, ventilatory-tracheostomy free survival) needed with phase III studies of longer duration. Setting: 25 NEALS centers in US

Abbreviations : ADE = adverse drug event; ADR = adverse drug reaction; ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALT = alanine transferase; ARR = absolute risk reduction; AST = aspartame transferase; ATLIS = Accurate Test of Limb Isometric Strength; CI = confidence interval; DB = double-blind; DBP = diastolic blood pressure; DSMB = Data Safety and Monitoring Board; FDA = Food and Drug Administration; g = gram; ITT = intention to treat; mITT = modified intention to treat; mmHg = millimeters of mercury; mo = month; N = number of subjects; NA = not applicable; NEALS = Northeast Amyotrophic Lateral Sclerosis Consortium; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PC = placebo-controlled; pts/mo = points per month; QoL = quality of life; RCT = Randomized controlled trial; SBP = systolic blood pressure; SVC = slow vital capacity; ULN = upper limit of normal; US = United States; VC = vital capacity.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form
riluzole	RILUTEK	ORAL	TABLET
edaravone	RADICAVA	INTRAVEN	PIGGYBACK
riluzole	TIGLUTIK	ORAL	ORAL SUSP
riluzole	EXSERVAN	ORAL	FILM
edaravone	RADICAVA ORS	ORAL	ORAL SUSP
riluzole	RILUZOLE	ORAL	TABLET
sod phenylbutyrate/taurursodiol	RELYVRIO	ORAL	POWD PACK

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 10, 2022

# ▲	Searches	Results
1	Riluzole/ae, tu [Adverse Effects, Therapeutic Use]	577
2	Edaravone/ae, tu [Adverse Effects, Therapeutic Use]	110
3	sodium phenylbutyrate.mp.	223
4	taurursodiol.mp.	12
5	3 and 4	12
6	1 or 2 or 5	689
7	limit 6 to (english and (adaptive clinical trial or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	175
8	Amyotrophic Lateral Sclerosis/dt, th [Drug Therapy, Therapy]	3923
9	limit 8 to (english language and guideline)	6
10	7 or 9	181
11	limit 10 to yr="2012 - 2023"	96

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RELYVRIO safely and effectively. See full prescribing information for RELYVRIO.

RELYVRIO (sodium phenylbutyrate and taurursodiol), for oral suspension
Initial U.S. Approval: 2022

---------- INDICATIONS AND USAGE ----------

RELYVRIO is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The recommended dosage is 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) administered orally or via feeding tube as follows: (2.1)
  - Initial dosage: 1 packet daily for the first 3 weeks (2.1)
  - maintenance dosage: 1 packet twice daily thereafter (2.1)
- Empty contents of one packet in a cup containing 8 ounces of room temperature water and stir vigorously prior to administration. (2.2)
- Take within 1 hour of preparation. (2.2)
- Administer RELYVRIO before a snack or meal. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

For oral suspension: 3 g sodium phenylbutyrate and 1 g taurursodiol in single-dose packets (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk in Patients with Enterohepatic Circulation Disorders, Pancreatic Disorders, or Intestinal Disorders: In patients with disorders that interfere with bile acid circulation, consider consulting with a specialist. Monitor for new or worsening diarrhea in these patients. These conditions may also lead to decreased absorption of either of the components of RELYVRIO. (5.1)
- Use in Patients Sensitive to High Sodium Intake: RELYRIO has a high sodium content. In patients sensitive to salt intake, consider the amount of daily sodium intake in each dose of RELYVRIO and monitor appropriately. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (at least 15% and at least 5% greater than placebo) are diarrhea, abdominal pain, nausea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amylyx Pharmaceuticals, Inc. at 877-374-1208 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

See Full Prescribing Information for complete list of clinically significant drug interactions. (7.1, 7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

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

Revised: 09/2022

Appendix 4: Key Inclusion Criteria

Population	Patients with ALS
Intervention	Medications in Appendix 1
Comparator	Medications in Appendix 1, placebo vs. sodium phenylbutyrate-taurursodiol
Outcomes	Mortality or time to permanent ventilation/tracheostomy, functional status, quality of life, adverse reactions
Timing	N/A
Setting	Outpatient

Edaravone (Radicava®™ or Radicava ORS®)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of edaravone in populations with clinically definite or probable amyotrophic lateral sclerosis
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- Up to 12 months

Requires PA:

- Edaravone (pharmacy and ~~physician~~ 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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
~~Is this a treatment for amyotrophic lateral sclerosis (ALS)?~~	~~**Yes**: Go to #534~~	~~**No:** Go to #4 Pass to RPh. Deny; medical appropriateness~~
3. Is the diagnosis a FDA approved indication ~~funded by OHP?~~	**Yes:** Go to #45	**No:** Pass to RPh. Deny; medical appropriateness ~~not funded by the OHP.~~
4. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	**Yes:** Go to #56	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6~~7~~	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have documented percent-predicted forced vital capacity (%FVC) ≥ 80%?	**Yes:** Record lab result. _____ Go to #7~~8~~	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥2 points in each of the 12 items?	**Yes:** Record baseline score. (0 [worst] to 48 [best]) _____ Approve for 6 months based on FDA-approved dosing. **(Table 1)***	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. ~~Is the medication being prescribed by or in consultation with a neurologist?~~	~~**Yes**: Go to #2~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

Renewal Criteria		
1. Has the prescriber provided documentation that the use of ~~Radicava (~~edaravone~~)~~ has slowed in the decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) with no decline more than expected given the natural disease progression (5 points from baseline over 6 months)?	**Yes:** Go to #2~~3~~	**No:** Pass to RPh. Deny; medical appropriateness Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."
2. Does the patient have documented percent-predicted forced vital capacity (%FVC) ≥ 80%?	**Yes:** Record lab result. Go to #3~~4~~	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there a documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥2 points in each of the 12 items?	**Yes:** Record score. (0 [worst] to 48 [best]) Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

~~* = see below for summary of FDA-approved dosage and administration. Consult FDA website for prescribing information details at www.fda.gov~~

~~***Dosage and Administration:***~~

Table 1. FDA Approved Dosing. (Consult FDA website for prescribing information details at www.fda.gov)

Edaravone (RADICAVA) intravenous solution	Edaravone (RADICAVA ORS) oral suspension
60 mg (two consecutive 30 mg infusion bags) IV infusion over 60 minutes	105 mg (5mL) taking orally or via feeding tube in the morning after overnight fasting. Food should not be consumed for 1 hour after administration except water.
• Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period • Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free period	

P&T/DUR Review: 4/23 (SF); 7/18 (DE)
Implementation: 8/15/18

Sodium Phenylbutyrate/Taurursodiol (Relyvrio™)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of sodium phenylbutyrate/taurursodiol.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacy 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 the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this a FDA approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have documented percent-predicted slow vital capacity (%SVC) ≥ 60% within past 6 months?	**Yes:** Record lab result. _____ Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score?	**Yes:** Record baseline score. _____ Approve for 6 months based on FDA-approved dosing.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the prescriber provided documentation that anticipated decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) has slowed in a clinically meaningful way?	**Yes:** Got to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Has the patient progressed to permanent ventilation or received a tracheostomy since beginning medication?	**Yes:** Pass to RPh; Deny; medical appropriateness.	**No:** Approve for 12 months.

P&T/DUR Review: 4/23 (SF)
Implementation: TBD