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 2nd, 2026 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	A. Gibler (OHA)
	E. Mental Health Clinical Advisory Group Update	A. Gibler (OHA)
	F. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Oncology Prior Authorization Updates	
	1. Public Comment	
	III. NEW BUSINESS	
1:30 PM	A. Analgesics Class Update	S. Servid (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
1:50 PM	B. Lynkuet® (elinzanetant) New Drug Evaluation	D. Moretz (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:05 PM	C. Hereditary Angioedema DERP Report	S. Fletcher (OSU)
	1. DERP Report/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:20 PM	D. GNRH Agonist and Antagonist Class Update Focused on Pelvic Pain and Dysmenorrhea	D. Moretz (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	

3. Discussion and Clinical Recommendations

2:40 PM	E. Waskyra™ (etuvetidigene autotemcel) Orphan Drug Evaluation 1. Orphan Drug Evaluation 2. Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	S. Fletcher (OSU)
2:55 PM	BREAK	
3:10 PM	F. Myalept® (metreleptin) Orphan Drug Evaluation 1. Orphan Drug Evaluation 2. Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:25 PM	G. Cephalosporins Literature Scan 1. Literature Scan 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
3:40 PM	H. Acne and Rosacea Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion and Clinical Recommendations	D. Moretz (OSU)
4:00 PM	IV. EXECUTIVE SESSION	
4:50 PM	V. RECONVENE for PUBLIC RECOMMENDATIONS	
	VI. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2028
Jennifer Henderson, DO	Physician	Asante Medical Director	Medford	December 2028
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2028
Bruce Leewiwatanakul, DO, MA	Physician	Child & Adolescent Psychiatry	Portland	December 2029

OREGON HEALTH AUTHORITY

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 5th, 2026
1:05 PM - 4:15 PM
Via Zoom webinar

MEETING MINUTES

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

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Bridget Bradley, PharmD; Douglas Carr, MD; Jennifer Henderson, DO; Russ Huffman, PMHNP; Eddie Saito, PharmD; Jeanne Savage, MD

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

Audience: Kyle Knudsen, Axsome Therapeutics; Kat Khachatourian, Novo Nordisk; Gene Kelly, Stealth BioTherapeutics; Miranda Ryzenman, Artia Solutions; Holly Jo Hodges, EOCCO/Moda Health; Andy Berg, Concis Labs; Gil Clifton, Stealth Bio; Gary Parenteau, Dexcom; Lee Stout, Chiesi; Jessica Garrison, Gainwell Technologies; Melissa Snider, Gilead; Norm Navarro, Providence; Becky Caswell, OHSU Health Services PBM; Bill McDougall, Biogen; Rosalie Elliott, UHA; Vivian Ton, UHA; Nirmal Ghuman, J&J; Chris Ferrin, IHN; Jennifer Davis, Gilead; Tammi Ocumpaugh, Otsuka; Rachel Peterson, PNWBD; Mariam Alboustani, Dyne Therapeutics; Aliethia McLeod, Trillium; Paul Thompson, Alkermes; Suzanne Morgan; Mark Kantor, AllCare; Lynda Finch, Biogen; Jill Carroll, BMS; William Lam; Daria Meleshkina, Moda EOCCO; Don Robinson, TN; Lewis Backus, OHA; Chris Demars, OHA; Leif Bruce, Novo Nordisk; Bill Branch; Cari Hall, Merck; Gloria Zepeda, AllCare; Dale Fisher, US; Ron Abraham; Brett Freund; Erin Nowak, AbbVie; Kate Landes; Melissa Vultaggio; Randy McCoy, Stealth Bio; Keith Boesen

(*) Provided verbal testimony

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. Stevens as Vice-Chair
ACTION: Motion to approve, 2nd, all in favor

D. Approval of Agenda and December 2025 Minutes presented by Roger Citron, RPh

ACTION: Motion to approve, 2nd, all in favor and Dr. Henderson abstained

E. Department Update: Andrew Gibler, PharmD

F. Mental Health Clinical Advisory Group Update: Andrew Gibler, PharmD

II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add Hyrnuo (sevabertinib) and Komzifti (ziftomenib) to Table 1 in the Oncology Agents PA criteria

B. Orphan Drug Policy Updates
Recommendation:
- Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Myqorzo (aficamten), Jascayd (nerandomilast), and Palsonify (paltusotine) based on their FDA-approved label
ACTION: Motion to approve, 2nd, all in favor

III. DRUG USE REVIEW (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

1. New Therapies for Treatment of Chronic Obstructive Pulmonary Disease

2. New Drugs for the Treatment of Uncomplicated Urinary Tract Infections

3. 2025 American College of Cardiology/American Heart Association Joint Committee Clinical Practice Guideline Update

IV. NEW BUSINESS

A. Antidepressant Class Update: Kathy Sentena, PharmD
Recommendations:
- No changes to the PDL are recommended based on review of the evidence
- Update PA criteria to allow for coverage of evidence supported indications for milnacipran
- Add at least one formulation of lithium and buspirone to the PDL to facilitate access to a 100-day supply
- Evaluate comparative costs in executive session
Public Comment: Kyle Knudsen, Axsome Therapeutics
ACTION: Motion to approve, 2nd, all in favor

B. Tryngolza (Olezarsen) New Drug Evaluation: Megan Herink, PharmD
Recommendations:
- Make olezarsen non-preferred in the "**Other Dyslipidemia Drug**" PDL class

- Implement **APOLIPOPROTEIN C-III (APOC3) Inhibitors** PA criteria to ensure appropriate use
ACTION: Modify proposed PA criteria to allow prescribing by or in consultation with a specialist for non-FCS indication, and define recent labs to be within past 6 months
Motion to approve, 2nd, all in favor

C. **Wegovy (semaglutide) Prior Authorization for MASH:** Sara Fletcher, PharmD
Recommendations:
- Update PA criteria for Wegovy (semaglutide)
- Evaluate comparative costs in executive session
Public Comment: Kat Khachatourian, Novo Nordisk
ACTION: Motion to approve, 2nd, all in favor

D. **Sedatives for Insomnia Class Update:** David Engen, PharmD
Recommendations:
- Remove PA for preferred products when there is no history of an opioid or sedative agent to allow for short-term use of up to 4 weeks
- Designate one sedative agent that is not from the benzodiazepine or GABA-A receptor agonist class as preferred
- Evaluate comparative costs in executive session
ACTION: Add BBT-I as an option for access
Motion to approve, 2nd, all in favor

E. **Medications for Allergies:** Deanna Moretz, PharmD
Recommendations:
- No changes to the PDL are recommended based on review of the evidence
- Create a PDL class for the **first-generation oral antihistamines**
- Remove PA for preferred nasal inhalers in adults
- Create a new PDL class, "**Ophthalmic Medications for Allergies**"
- Make at least one product preferred without prior authorization
- Evaluate comparative costs in executive session
ACTION: Motion to approve, 2nd, all in favor

F. **Forzinity (elamipretide) Abbreviated New Drug Evaluation**: Sarah Servid, PharmD
Recommendations:
- Implement proposed **Elamipretide** PA to require documentation of genetic testing and supportive care for heart failure
ACTION: Motion to approve, 2nd, all in favor

IV. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Samara Stevens, ND; Douglas Carr, MD; Jennifer Henderson, DO; Russ Huffman, PMHNP; Eddie Saito, PharmD

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

V. RECONVENE for PUBLIC RECOMMENDATIONS

A. Antidepressant Class

Recommendation: Make venlafaxine tablets ER 24 hours preferred; make lithium carbonate capsules, tablets and tablet ER preferred; make buspirone tablets preferred; and make lithium citrate solution, Lithobid, and Bucapsol voluntary non-preferred

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

B. Wegovy® (semaglutide) for MASH

Recommendations: Remove Ozempic step through for Wegovy for patients who do not have diabetes

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

C. Sedatives for Insomnia Class

Recommendations: Make Belsomra (suvorexant) preferred

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

D. Medications for Allergies

Recommendations: Make generic oral hydroxyzine pamoate capsules, hydroxyzine tablets, cyproheptadine tablets, diphenhydramine tablets, diphenhydramine capsules, chlorpheniramine tablets, diphenhydramine liquid, and cyproheptadine syrup preferred and all other first generation oral antihistamines non-preferred; make levocetirizine, desloratadine, and fexofenadine tablets and cetirizine solution preferred; make azelastine nasal allergy inhaler preferred; make cromolyn, azelastine, and olopatadine legend ophthalmic drops preferred and all other ophthalmic products nonpreferred

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

VI. ADJOURN – Meeting concluded at approximately 4:20 p.m.

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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
amivantamab/ hyaluronidase-lpuj	RYBREVANT FASPRO

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Populations:

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

Covered Alternatives:

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

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

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

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

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

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

Table 1. Oncology agents which apply to this policy (Updated 3/3/2026)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting.
Biosimilars for drugs on this list are included in the policy but may not be specifically listed.

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

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

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

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

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

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

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Drug Class Update: Analgesics

Date of Review: April 2026

Date of Last Review: Non-steroidal anti-inflammatory drugs (February 2021)
Opioids (April 2021)
Muscle relaxants (September 2019)
Topical Pain Medications (August 2020)
Suzetrigine (June 2025)
Dates of Literature Search: 01/01/2021 – 02/13/2026

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

Purpose for Class Update:
Evaluate new comparative evidence of oral analgesics (opioids and non-opioids) including evidence for pain conditions that are currently unfunded.

Plain Language Summary:

- Many social and medical factors contribute to acute and chronic pain. In most cases, pain should be treated with more than one type of treatment with the goal of reducing, not eliminating, pain.
- Common types of medicines used to treat pain include non-steroidal anti-inflammatory medicines (NSAIDs), acetaminophen, opioids, muscle relaxants, suzetrigine, and topical pain medicines that are applied to the skin. Evidence shows that medicines also used for depression or seizures can improve certain types of pain.
- There is little evidence that one specific medicine improves pain more than another medicine of the same type.
- New evidence showed that certain types of pain medicines may have benefit over other types of pain medicines for specific people:
  - NSAIDs may be more effective compared to acetaminophen for acute pain after surgery in children or compared to opioids after breast surgery in adults.
  - Most medical organizations recommend antidepressants as an initial treatment option for pain lasting longer than 3 months.
  - When opioids are prescribed for long-term pain treatment (>3 months) they can cause serious side effects and may worsen pain.
  - Medicines for seizures or depression can improve nerve pain.
  - NSAIDs can improve pain caused by swelling in conditions like gout or arthritis.
- For people already taking opioids long-term for chronic pain, patients and providers should discuss risks and benefits for gradual dose reduction and develop a plan to manage pain and risks related to opioids. Evidence shows that gradual dose reduction of opioids is most successful when offered with high intensity support programs involving multiple providers and treatments.

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Research Questions:

1. What is the comparative efficacy and effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, acetaminophen, suzetrigine, muscle relaxants, and topical medications for acute and chronic pain?
2. What are the comparative harms of NSAIDs, opioids, muscle relaxants, and topical medications for acute and chronic pain?
3. Are there subgroups of patients based on demographic characteristics (e.g., age, race, ethnicity, socioeconomic status), concurrent medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of NSAIDs, opioids, muscle relaxants, and topical medications for acute and chronic pain?

Conclusions:

Acute pain

- In acute post-operative pain in children and adolescents,
    - ibuprofen had small improvements in pain intensity with 24 hours following surgery compared to acetaminophen (moderate certainty evidence).[1]
    - ibuprofen was associated with fewer adverse events than opioids (moderate certainty evidence) or ketorolac (low certainty evidence).[1]
    - diclofenac was associated with less nausea/vomiting but increased risk of bleeding compared to opioids (moderate certainty evidence).[2]
- In acute post-operative pain related to breast surgery, NSAIDs may reduce pain intensity within 24 hours, reduce need for rescue opioid use, and decrease risk of nausea/vomiting compared to opioids (low to moderate certainty evidence).[3] NSAIDs use was not associated with risk of breast hematomas compared to opioids (low certainty evidence).[3]
- There was no new comparative evidence identified for suzetrigine in post-operative pain or other acute pain conditions.
- For treatment of acute gout flares, non-selective NSAIDs (e.g., indomethacin, naproxen) have similar symptom improvement compared to selective COX-2 inhibitors (e.g., celecoxib) or glucocorticoids (low to moderate certainty evidence), but may be associated with more adverse gastrointestinal adverse events and withdrawals due to adverse events (moderate certainty evidence).[4]
- In pain related to acute otitis media, there is insufficient evidence to determine differences in efficacy or safety between ibuprofen or acetaminophen.[5]
- In infants who use ibuprofen or acetaminophen as needed for acute treatment of fever or pain during the first year of life, there is no difference in the incidence of eczema or bronchiolitis at 1 year (moderate quality evidence).[6]
- In acute low back pain (<4 weeks in duration), NSAIDs are recommended by the Veterans Administration/Department of Defense (VA/DOD) and National Institute for Health and Care Excellence (NICE).[7,8]

Cancer-related Pain

- In people with pain related to cancer, there is no difference in pain relief with controlled-release oxycodone and controlled-release morphine (low certainty evidence).[9] There was insufficient evidence to evaluate differences in safety or efficacy between other opioids.[9,10]

Chronic Pain (typically defined as pain lasting longer than 3 months)

- There was insufficient evidence to compare efficacy or safety of specific agents within each class of medications for treatment of chronic pain. Guidelines include recommendations based on medication class or for specific agents that had supporting evidence of benefit. For chronic pain, medications should be offered in conjunction with non-pharmacologic and psychologic therapies.
- Antidepressants

- The Scottish Intercollegiate Guidelines Network (SIGN) recommends duloxetine in people with chronic non-cancer pain, and the VA/DOD recommends duloxetine for chronic low back pain.[8,11]
- NICE recommends antidepressants (specifically amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline) in adults with chronic primary pain.[12]
- NICE recommends duloxetine or amitriptyline for chronic neuropathic pain, and the American Academy of Neurology (AAN) recommend serotonin norepinephrine reuptake inhibitors (SNRIs; duloxetine, venlafaxine, and desvenlafaxine) or tricyclic antidepressants (TCAs; amitriptyline, nortriptyline, imipramine) for treatment of painful diabetic neuropathy.[13,14]

- Opioids
  - Guidelines from multiple organizations recommend against offering opioids for all types of chronic non-cancer pain.[7,8,12-18] Direct and indirect evidence suggests that individual opioids are similarly ineffective for chronic pain management (low to very low certainty evidence).[18]
  - Use of opioids up to 3 months should be prescribed only when alternatives have been fully explored and benefits outweigh risks.[7,14,18]
  - When opioids are prescribed, appropriate monitoring, risk mitigation strategies, frequent evaluations, and patient-centered collaborative approaches to medication tapers are recommended.[16,18,19] Consider prescribing naloxone for people prescribed opioids who may be at risk of an opioid overdose. When available, interdisciplinary or multidisciplinary care, or multimodal approaches that emphasizes non-pharmacological and self-management strategies to deprescribe opioids are recommended.[16,18,19]
  - In people with severe opioid use disorders (OUD), there is moderate quality evidence that deprescribing alone, without access to long-term substance use disorder treatment and care, is associated with increased risk of overdose and death.[19]
  - For people on chronic daily opioids, the VA/DOD suggest use of buprenorphine instead of a full opioid agonists because of potential for lower risk of overdose or misuse (weak recommendation for treatment).[16]
- Muscle relaxants
  - Guidelines from VA/DOD suggest against offering muscle relaxants for chronic low back pain lasting longer than 4 weeks.[8]
  - NICE recommends baclofen as an initial treatment option for spasticity and pain related to multiple sclerosis (MS).[17]
- NSAIDs
  - The American Academy of Orthopedic Surgeons (AAOS) recommends topical or oral NSAIDs for adults with knee osteoarthritis to improve pain and function.[15]
  - The VA/DOD and NICE recommend NSAIDs for acute or chronic low back pain lasting longer than 4 weeks.[7,8] Because of risk for adverse events with chronic use, they recommend the lowest effective dose for the shortest time with appropriate monitoring and gastroprotective treatment (e.g., antacid medications).[7]
  - NICE recommends against use of NSAIDs for chronic primary pain.[12]
- Other topicals
  - For neuropathic pain, capsaicin is an alternative option for people who cannot tolerate oral therapies (low certainty evidence).[13,14]
- Antiepileptics
  - NICE recommends against use of antiepileptics for chronic primary pain or low back pain.[7]
  - NICE recommends carbamazepine for initial treatment of trigeminal neuralgia.[13]
  - NICE and AAN recommend gabapentinoids (e.g., gabapentin, pregabalin) as initial treatment for neuropathic pain or peripheral diabetic neuropathy.[13,14] AAN also recommends sodium channel blocker antiepileptics (e.g., carbamazepine, oxcarbazepine, lamotrigine, valproic acid, lacosamide) as initial treatment in painful diabetic neuropathy based on moderate certainty evidence.[14] NICE recommends against antiepileptics for neuropathic pain unless prescribed in consultation with a specialist.[13]

- NICE recommends gabapentin as a second-line treatment (e.g., after trial of a muscle relaxant) in people with spasticity and pain related to multiple sclerosis.[17]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the clinical evidence. Evaluate costs in executive session.
- Update opioid, NSAID, and muscle relaxant prior authorization (PA) criteria to align with current evidence for chronic pain conditions (**Appendix 1**).

Summary of Prior Reviews and Current Oregon Health Plan (OHP) Fee-for-service (FFS) Policy:

- Muscle relaxants:
  - Previous reviews did not show differences in the clinical efficacy between skeletal muscle relaxants for musculoskeletal conditions.
  - Evidence is insufficient to draw firm conclusions regarding the comparative effectiveness between baclofen, tizanidine or dantrolene for spasticity.
  - The skeletal muscle relaxants tizanidine, cyclobenzaprine, and baclofen are more efficacious than placebo for short-term (5 to 7 days) pain relief of acute low back pain.
  - Dantrolene and chlorzoxazone are associated with rare serious dose-related hepatotoxicity.
  - There is no evidence to support using baclofen for alcohol use disorder (AUD) based on a high-quality systematic review and meta-analysis.
  - Non-preferred muscle relaxants require PA every 3 months because of insufficient evidence for long-term use. The use of carisoprodol is limited to an equivalent of a two-week supply (56 tablets), which is consistent with prescribing information, every 90 days. Prior authorization criteria are also in place to prevent the use of carisoprodol with opioids due to safety concerns.
- NSAIDs:
  - Compared to placebo, there is evidence that NSAIDs improve chronic pain and function in people with osteoarthritis (OA) and inflammatory arthritis (e.g., rheumatoid arthritis). In acute and chronic low back pain, NSAIDs improve pain compared to placebo, but differences are small and unlikely to be clinically meaningful. Multiple organizations including American College of Physicians (ACP), VA/DOD, and NICE recommend use of NSAIDs for low back pain.
  - There is evidence of no differences in efficacy between specific NSAIDs when treating low back pain or ankylosing spondylitis. In patients with acute soft tissue injuries, there is no clinically meaningful difference in efficacy between NSAIDs and acetaminophen or NSAIDs and opioids, based on moderate to high quality of evidence.
  - There are PA criteria for non-preferred products and for ketorolac use beyond 5 days.
- Opioids
  - Evidence supports modest improvements in pain and function with use of opioids for acute pain or chronic non-cancer pain compared to placebo (high-quality evidence). No difference in pain or functional status has been consistently observed between opioids and non-opioid analgesics for chronic non-cancer pain (low to moderate quality evidence).
  - There is moderate quality from direct and indirect evidence that buprenorphine provides similar reduction in pain intensity with short-term use (less than 6 months) compared to other opioids and low quality evidence that buprenorphine is not safer than other opioids for treatment of chronic pain.
  - Evidence is limited by short follow-up and exclusion of patients at high risk for adverse events, such as opioid overdose and death. Current high-quality guidelines recommend opioid therapy be reserved for patients with proven medical necessity and those who have failed non-opioid analgesic therapy. Chronic opioid therapy should only be considered with documented improvement in pain and function, thorough assessment of risks and benefits of therapy, and with appropriate ongoing monitoring.

- PA criteria limit short-acting opioid prescriptions to 7 days and no more than 90 milligram morphine equivalents (MME) per day. Quantity limits allow up to 2 prescriptions every 90 days without PA. All prescriptions for long-acting opioids require PA. For authorization of chronic opioid therapy, providers are required to document sustained improvement from treatment, review the prescription drug monitoring program (PDMP) to verify appropriate prescribing patterns, conduct a recent urine drug screen to assess use of illicit drugs, and assess risk of concurrent central nervous system depressants.

- Topical pain medications
  - Compared to placebo, evidence shows topical NSAIDs improve acute and chronic musculoskeletal pain, but do not differ in efficacy compared to oral NSAIDs for pain related to knee osteoarthritis (low quality evidence). Topical capsaicin (8%) improves postherpetic neuralgia and human immunodeficiency virus (HIV)-neuropathy, but not diabetic peripheral neuropathy compared to low dose capsaicin (0.04%) or placebo. There is insufficient evidence for topical salicylate, low-concentration (0.04%) capsaicin, and topical lidocaine in acute or chronic pain conditions.
  - The 2019 American College of Rheumatology/Arthritis Foundation strongly recommends topical NSAIDs for knee OA and conditionally recommends topical NSAIDs for hand OA. Topical low-concentration (0.04%) capsaicin is conditionally recommended for patients with knee OA and conditionally recommended against use in patients with hand OA.
  - PA is required for non-preferred products. Lidocaine patches are limited to evidence-supported indications and quantities.
- Suzetrigine
  - Compared to placebo, suzetrigine, a new oral sodium channel blocker, improves pain intensity from 0 to 48 hours after bunionectomy and abdominoplasty (moderate certainty evidence).[20]
  - There is moderate certainty evidence that suzetrigine is not superior to low dose hydrocodone 5 mg/acetaminophen 325 mg given every 6 hours after bunionectomy or abdominoplasty as evaluated by the time-weighted sum of the pain intensity between hours 0 and 48 (SPID48) on the numeric pain rating scale.[20]
  - There is moderate quality evidence that suzetrigine is safe for use for 48 hours, and insufficient evidence based on one open-label, single arm study that suzetrigine is safe for use up to 14 days (mean 9.8 days).[20]
  - Suzetrigine is available without PA for up to 48 hours, and covered with prior authorization for up to 14 days for acute pain management. Use of an opioid is not required for authorization of suzetrigine.

Background:

Pain is a common condition that is associated with significant impacts on quality of life, lost work productivity, and healthcare costs. Pain can be classified as acute (generally defined as less than 1 month in duration), subacute (1-3 months in duration), or chronic (>3 months in duration).[21] Acute and subacute pain is generally caused by an injury or response to an underlying disease process. Treatment and management of underlying conditions, when identified, are essential for pain management. Chronic pain can be further classified as secondary chronic pain (based on an underlying medical condition or injury) or primary chronic pain if it is pain is unrelated to a known cause. Untreated acute pain can evolve into chronic pain, and both primary and secondary chronic pain can coexist. Because pain is a clinically complex condition influenced by a wide range of biological, psychological and social factors, treatments for pain also cover a broad range of non-pharmacologic and pharmacologic interventions.

Choice of medication treatment options can depend on treatment setting (inpatient or outpatient), underlying cause or type of pain, duration of pain, risk for adverse events, and individual patient factors. Examples of outpatient medications used for pain management include NSAIDs, acetaminophen, antidepressants (e.g., SNRIs, TCAs), antiepileptics (e.g., gabapentin, pregabalin, carbamazepine), opioids, muscle relaxants, topical pain medications (e.g., capsaicin, lidocaine, NSAIDs), and suzetrigine. Local or regional anesthesia (e.g., anesthetic injections, epidurals, nerve blocks and continuous wound infiltration) is also commonly

used for surgical procedures.[22] In 2025, the Oregon legislature passed senate bill 598 which requires the Pharmacy & Therapeutics (P&T) committee, in making recommendations to the Oregon Health Authority, "ensure there is at least one clinically appropriate non-opioid prescription drug available as an alternative for each opioid prescription drug and ensure the utilization controls and prior authorization requirements are no more restrictive for the non-opioid prescription drug than the utilization controls and prior authorization requirements for the opioid prescription drug". This senate bill defines "clinically appropriate" as use "supported by nationally recognized compendia, clinical guidelines or generally recognized standards of care." Most guidelines for both acute and chronic pain recommend a multimodal approach to pain management.[12,16,18,23] Interventions may include patient education, psychological management, medications, and non-pharmacologic treatments. In acute pain, including pain related to surgeries, this multimodal approach is intended to manage pain, decrease stress responses, reduce reliance on any single agent in order to minimize adverse effects, and assist patients in returning to normal function.[22] In chronic pain, a multimodal approach can help address maladaptive thought processes and comorbid conditions that contribute to pain in order to improve daily function and decrease the impact that pain has on quality of life.[24] Non-pharmacologic treatments for pain management encompass a wide range of physical interventions (such as physical therapy, massage, temperature therapy, exercise, or acupuncture) and psychological interventions (such as cognitive behavioral therapy, mindfulness meditation, acceptance and commitment therapy, or progressive muscle relaxation).[7,12,16,18] Care should include education on sleep, nutrition, stress reduction, mood, exercise, and knowledge of pain.

For the management of chronic pain, current evidence has not demonstrated clinically significant differences in pain or function between classes of analgesics or individual agents. Recommended treatments for chronic primary pain (i.e., pain unrelated to an underlying condition) include antidepressants and non-pharmacotherapy, including physical and psychological interventions.[8,16,18] In people with chronic pain, antidepressants may help with quality of life, pain, sleep and psychological distress, even in the absence of a diagnosis of depression.[12] Certain antiepileptic medications like gabapentinoids (e.g., pregabalin, gabapentin) have evidence of benefit for some specific types of neuropathy such as postherpetic neuralgia and diabetic neuropathy, but mixed evidence of benefit for other types of off-label neuropathic pain.[13,14] Opioids are not routinely recommended for management of chronic non-cancer pain because they are associated with serious long-term harms including increased risk of overdose and development of substance use disorder and have not been associated with clinically significant improvements in pain intensity or function with long-term use.[16,18,25] Evidence suggests that long-term use of opioids may worsen chronic pain and decrease function compared to treatment with non-opioid medications.[18]

Acute pain management is typically tailored for conditions in which there is evidence of benefit. For example, there is evidence to support NSAIDs for inflammatory conditions like arthritis, gout, tendinitis, pelvic pain, and dysmenorrhea. In post-operative pain, 2016 guidelines from the American Pain Society include recommendations for opioids, acetaminophen, NSAIDs, and gabapentinoids as part of a multimodal approach to pain management.[23] Suzetrigine, a newer non-opioid analgesic approved after publication of these guidelines, also has evidence in acute pain management after surgery.[26] Muscle relaxants have some evidence of benefit with short-term use in patients with low back pain or spasticity, but very limited data on long-term use.[8,17] Similarly, acetaminophen, opioids, and NSAIDs have evidence of benefit in a variety of other acute pain conditions, but also evidence of harms with high doses, long-term therapy, or in people with pre-existing conditions which may increase risk of adverse events. Opioids are associated with risk of dependence, addiction, abuse, misuse, neonatal withdrawal syndrome, overdose, respiratory depression, and death.[16,25] NSAIDs are associated with increased risk of gastrointestinal and cardio-renal adverse events, and acetaminophen has been associated with hepatotoxicity with high doses, concomitant alcohol, or underlying liver disease. For people who are currently on treatments for chronic pain management that have little evidence of benefit, but potential harms, most guidelines recommend an individualized, patient-centered approach to assess benefits, educate patients on risks related to ongoing therapy, and develop strategies for monitoring and risk mitigation if therapy is continued.[12,16,19] When available, interdisciplinary or multidisciplinary care, or multimodal approaches that emphasizes non-pharmacological and self-management strategies are recommended to deprescribe opioids and manage chronic pain.[16,18,19]

In most cases, the goals of pain treatment are to reduce rather than eliminate pain, to improve function, and to reduce the impact pain has on quality of life. Outcomes in clinical trials include assessments of pain intensity (typically via numeric rating scales), physical functioning, emotional functioning, and patient ratings for overall improvement.[18] Validated self-reported questionnaires include the Brief Pain Inventory or Multidimensional Pain Inventory for physical functioning and the Beck Depression Inventory or the Profile of Mood States for emotional functioning.[18] Systematic reviews and guidelines often aggregate data using standardized mean differences (SMD) when pain intensity or functioning has been reported using a variety of rating scales in clinical trials. SMDs of 0.2, 0.5 and 0.8 typically correspond to small, medium and large effect sizes.[27] SMDs less than 0.2 probably represent a clinically insignificant change.[27]

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

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

New Systematic Reviews:
A 2024 Cochrane systematic review evaluated efficacy and safety of ibuprofen in acute postoperative pain in children and adolescents under 18 years of age.[1] A literature search through August 2023 identified 43 RCTs (n=4,265) that compared ibuprofen to placebo, acetaminophen, opioids, or other NSAIDs.[1] Studies enrolled between 23 and 741 participants, and only 5 RCTs enrolled participants with a mean age less than 3 years old.[1] Surgeries included both inpatient and ambulatory outpatient surgeries. Ibuprofen was administered orally in 20 of the 23 studies during the preoperative (n=23), intraoperative (n=4), postoperative periods (n=6). Ten RCTs evaluated administration during multiple time periods (n=10).[1] No studies evaluated the prespecified primary outcome of pain relief (≥ 50% improvement in pain intensity). Certainty in the evidence was significantly limited by lack of adequately reported methods and outcomes (37 studies had high or unclear risk of bias in one or more domains).[1]

- Twenty-one studies compared ibuprofen and acetaminophen. Compared to acetaminophen, ibuprofen improved pain intensity by a small amount within 2 hours post-surgery (SMD −0.42, 95% confidence interval [CI] −0.82 to −0.02; 2 RCTs, n=100; moderate-certainty evidence) and at 2 to 24 hours post-surgery (SMD −0.21, 95% CI −0.40 to −0.02; 6 RCTs, n=422 ; low-certainty evidence).[1]
- Two studies evaluated ibuprofen compared to morphine or ketorolac, but did not report outcomes of pain intensity or serious adverse events between groups. Overall adverse events within 7 days of the procedure were less frequent with ibuprofen compared to morphine (relative risk [RR] 0.58, 95% CI 0.40 to 0.83; risk difference [RD] −0.25, 95% CI −0.40 to −0.09; number needed to treat [NNT] 4; 1 RCT, n=154; moderate-certainty evidence) and ketorolac (RR 0.51, 95% CI 0.27 to 0.96; RD −0.29, 95% CI −0.53 to −0.04; NNT 4; 1 RCT, n=59; low certainty evidence).[1]

A 2023 Cochrane systematic review evaluated efficacy and safety of diclofenac in acute postoperative pain in children and adolescents under 18 years of age.[2] The average age of participants ranged from 2.1 to 14.3 years.[2] The review included 32 RCTs (n=2250) that compared diclofenac to placebo (n=3), opioids (n=7), acetaminophen (n=5), bupivacaine (n=5) or other pharmacotherapy (n=10).[2] All surgeries were performed under general anesthesia. The most common types of

procedures included tonsillectomies (n=9), strabismus surgeries (n=6); inguinal herniotomies (n=4), appendectomies (n=4), and dental surgeries (n=2).[2] Diclofenac was administered through a variety of routes (rectal, intravenous, ophthalmic, oral, and topical) and was administered preoperatively (n=21), intraoperatively (n=2), and postoperatively (n=9).[2] The prespecified primary outcome was pain relief (≥ 50% improvement in pain intensity); secondary outcomes included pain intensity, adverse events, and serious adverse events.[2] Most studies had high or unclear risk of bias in one or more domains which significantly limited evaluation of evidence and confidence in treatment effects.[2]

- Evidence was graded as very low certainty for pain improvement for all comparisons indicating significant uncertainty in the magnitude of benefit for diclofenac compared to placebo or other analgesic therapy.[2]
- Compared to opioids, there is moderate certainty evidence that diclofenac probably reduces nausea/vomiting (41.0% in opioids, 31.0% in diclofenac; RR 0.75, 95% CI 0.58 to 0.96; 7 RCTs, n=463) and increases risk of any bleeding (5.4% in opioids, 16.5% in diclofenac; RR 3.06, 95% CI 1.31 to 7.13; 2 RCTs, n=222).[2]

A 2021 Cochrane systematic review evaluated perioperative use of NSAIDs during breast surgery.[3] The review identified 12 RCTs (n=1596) which compared NSAIDs to placebo/no treatment (n=8) or an opioid (n=4).[3] NSAIDs included in these studies were diclofenac, ibuprofen, ketorolac, flurbiprofen, parecoxib, and celecoxib. Types of surgeries included breast augmentation surgery, mastectomy, and lumpectomy.[3] Of the studies which compared NSAIDs to opioids, one studied preoperative administration and 4 studied postoperative administration.[3] All except one study had high or unclear risk of bias in one or more domains.[3]

- Compared to placebo, there was low certainty evidence that NSAIDs reduce pain intensity (SMD -0.26, 95% CI -0.49 to -0.03; 3 RCTs, n=310; I^2 = 73%) and opioid use (SMD -0.45, 95% CI -0.85 to -0.05; 4 RCTs, n=304; I^2 = 63%) within 24 hours following surgery.[3] There was little to no difference in the incidence of breast hematomas within 90 days (low certainty evidence) compared to placebo, and evidence for other adverse events was very uncetain.[3]
- Compared to an opioid (e.g., morphine, hydrocodone, hydromorphone, fentanyl), NSAIDs may reduce pain intensity (SMD -0.68, 95% CI -0.97 to -0.39; 3 RCTs, n=200; I^2 = 89%; low-certainty evidence), reduce opioid use (SMD -6.87, 95% CI -10.93 to -2.81; 3 RCTs, n=178; I^2 = 96%; low-certainty evidence), and decrease risk of nausea and vomiting within 24 hours of surgery (RR 0.18, 95% CI 0.06 to 0.57; 3 RCTs, n=128; I^2 = 0%; moderate-certainty evidence).[3] There was little to no difference in the incidence of breast hematomas within 90 days (low certainty evidence) compared to opioids, and evidence for other adverse events was very uncertain.[3]

A 2021 Cochrane systematic evaluating NSAIDs for acute gout identified 28 RCTs (n=3406) compared to placebo, another NSAID, glucocorticoids, or other drug treatment.[4] The average age in the included studies ranged from 44 to 66 years with an average disease duration ranging from 5 to 17 years.[4] Most participants had a single joint affected. Of the 9 trials which enrolled participants regardless of number of joints involved, 66% to 96% had monoarthritis.[4] Included study durations ranged from 4 to 14 days. Most RCTs had unclear or high risk of bias; only 2 RCTs had low risk in all domains.[4]

- Upon comparison of a nonselective NSAID (indomethacin) to a selective COX-2 inhibitor in 6 RCTs (n=1244), there was no difference in pain intensity, inflammation, treatment success (moderate certainty evidence), quality of life, or function (low certainty evidence).[4] The COX-2 inhibitors included celecoxib and other COX-2 inhibitors not available in the US. Indomethacin was associated with increased risk of total adverse events, most commonly gastrointestinal events (mean difference [MD] 21.7%; 95% CI 8.3 to 41.1; number needed to harm [NNH] 5), and withdrawals due to adverse events (MD 3.9%; 95% CI 1% to 9%; NNH 26) compared to selective COX-2 inhibitors (moderate certainty evidence).[4]
- Compared to glucocorticoids (e.g., prednisolone), NSAIDs (e.g., indomethacin or naproxen) did not show a difference in pain intensity, function, treatment success, withdrawals due to adverse events (moderate certainty evidence) or inflammation (low certainty evidence) in short term studies (4-14 days).[4] NSAIDs were probably associated with increased risk of any adverse event compared to glucocorticoids but with significant heterogeneity and imprecision (MD 32.3%; 95% CI 1.6 to 80.8%; NNH 5; 5 RCTs; moderate certainty evidence).[4]

A 2023 Cochrane systematic review evaluated acetaminophen or NSAIDs for pain related to acute otitis media in children.[5] The review included 4 RCTs which compared acetaminophen or ibuprofen to placebo or each other over 1 to 7 days.[5] Of the included studies, 3 RCTs enrolled participants less than 7 years of age.[5] One study prescribed concurrent antibiotics, and another allowed antibiotics at the discretion of the prescribing provider.[5]

- Compared to placebo, pain relief at 48 hours was improved with acetaminophen (children with pain: acetaminophen 10%, placebo 25%; RR 0.38, 95% CI 0.17 to 0.85; NNT 7, low-certainty evidence) and ibuprofen (children with pain: ibuprofen 7%, placebo 25%; RR 0.28, 95% CI 0.11 to 0.70; NNT 6; low-certainty evidence).[5] There was insufficient evidence to evaluate fever and adverse events for both drugs.[5]
- Four RCTs evaluated ibuprofen versus acetaminophen with no differences found between the two treatments for ear pain, mean pain score, fever or adverse events over 1 to 7 days.[5] Evidence was graded as low or very low quality, indicating significant uncertainty in the magnitude of benefit or incidence of adverse events between groups.[5]
- Two trials compared the combination of ibuprofen and acetaminophen to acetaminophen alone, but evidence was limited by small study sizes and imprecise estimates leading to substantial uncertainty in treatment effects (very low certainty evidence).[5]

A 2022 Cochrane systematic review evaluated oxycodone compared to alternative analgesics for cancer-related pain.[9] The review included 42 studies (n=4485) with an average age for enrolled participants ranging from 45 to 75 years.[9] Length of treatment ranged from a single dose to 12 months, and most trials enrolled participants with a variety of cancer types.[9]

- Most included RCTs (n=24) compared controlled-release formulations of oxycodone and morphine.[9] There was no difference between groups in the number of participants who achieved significant pain relief (low certainty evidence). There was low certainty evidence that controlled-release morphine may have a small, but clinically insignificant, improvement in pain intensity compared to controlled-release oxycodone (difference 0.27 points on a 0-10 point scale; SMD 0.14, 95% CI 0.01 to 0.27; n = 882; 7 RCTs; n=882).[9] These differences were not apparent following sensitivity analyses and exclusion of studies published in Chinese that had unclear risk of bias from lack of reported methods.[9] There was no difference in drowsiness/sedation or nausea between oxycodone and morphine (low certainty evidence) and estimates of effect for other adverse events were very uncertain.[9]
- The review included RCTs that directly compared many other types and formulations of opioids, but evidence was graded as very low certainty for all comparisons and outcomes indicating significant uncertainty in the magnitude of benefit or incidence of adverse events between different opioids.[9]

A 2021 Cochrane systematic review evaluated hydromorphone for cancer-related pain and identified 8 RCTs which compared hydromorphone to other analgesics, including oxycodone, morphine, and fentanyl.[10] There was no clear difference in pain intensity between hydromorphone and other analgesics.[10] Evidence for all efficacy and safety outcomes was graded as very low quality indicating significant uncertainty in the magnitude of benefit or incidence of adverse events between groups.[10]

After review, 37 systematic reviews were excluded due to poor quality (e.g, indirect network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Systematic reviews that were used for the development of one of the high-quality guidelines described below are not described separately.

New Guidelines:

Chronic Pain:

In 2021, NICE published recommendations for chronic primary pain management defined as pain that persists for more than 3 months and has no underlying condition that adequately accounts for the pain.[12] Chronic primary pain and chronic secondary pain (due to an underlying condition) can coexist. Pharmacologic treatment recommendations for chronic primary pain include:

- Consider an antidepressant (specifically amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline) for people over 18 years of age or people 16 to 17 years of age with specialist consultation.[12] These medicines may help with quality of life, pain, sleep and psychological distress, even in the absence of a diagnosis of depression.
- Do not initiate the following medicines for chronic primary pain in adults as these medications have not consistently demonstrated benefit for chronic primary pain and may be associated with harms: antiepileptics including gabapentinoids, antipsychotics, benzodiazepines, corticosteroid trigger point injections, ketamine, local anesthetics (topical or intravenous), local anesthetic/corticosteroid combination trigger point injections, NSAIDs, opioids, or acetaminophen.[12]
- For people with chronic primary pain already taking one of the medicines listed above that lack evidence of effectiveness, providers should review prescribing as part of shared decision making to educate patients on lack of evidence in chronic primary pain, develop a shared plan for continued safe prescribing if individual benefits outweigh harms, or encourage and support the patient to reduce or stop the medicine when possible if there is little benefit or significant harm.

In 2025, SIGN issued guidance on management of chronic pain (also defined as pain lasting longer than 3 months).[18] Part 1 of this guideline covers recommendations for opioids, naloxone, antidepressants, medicinal cannabis, pain management programs, psychological interventions, self-help interventions and occupation-based interventions. Recommendations for muscle relaxants, simple analgesics, topical analgesics, anti-epileptics, combination therapies will be subsequently published in Part 2 of the guideline. Recommendations were supported by multiple high-quality systematic reviews.

Recommendations for non-pharmacologic therapy include:[18]

- Following appropriate assessment, consider comprehensive pain management programs for people with chronic pain. Pain management programs are comprised of multiple interventions delivered concurrently (typically in a group setting over several sessions or weeks) including psychological interventions (e.g., cognitive behavioral therapy, talk therapy), medication review, pain education, and exercise or physical activity.
- Offer cognitive behavioral therapy (either face-to-face or remotely) for adults with chronic pain.
- Consider face-to-face acceptance and commitment therapy for chronic pain when there is a preference for an acceptance approach.
- Consider mindfulness-based stress reduction for chronic pain when there is a preference for mindfulness approach.
- Consider peer support interventions or digital self-management interventions as part of the holistic and individualized management for people with chronic musculoskeletal pain.

Table 1 describes medication recommendations for opioids, naloxone and antidepressants for chronic pain.

Table 1. SIGN recommendations for use of medications in chronic pain[18]

Recommendations	Supporting Evidence
Opioids	
- Do not routinely consider opioids for people with chronic non-malignant pain. - Short-term use of opioids (up to 3 months) may be prescribed only	- Several high-quality systematic reviews have consistently found either no benefit with opioids in pain severity or function, or only small reductions in pain severity that do not meet thresholds for clinical efficacy, compared to placebo in short-term trials over 1 to 6 months duration (high certainty evidence).

when other therapies have been fully explored and if potential benefits outweigh risks of serious harms. - When opioids are prescribed, re-assess benefits and risks early and frequently. Adjust dose and discontinue treatment if clinically indicated. - Regularly review opioid doses over 50 MME/day (at least annually and preferably more often) to detect emerging harms or efficacy. - Consultation or review by a pain specialist should be performed when doses exceed 90 MME/day.	- When evaluating only 3- to 6-month trials, no difference in pain intensity or pain response between opioids and placebo are found. Evidence from observational studies suggest that pain-related and functional outcomes may be worse with long-term opioid use (>12 months) compared to not taking opioids. - High-quality network meta-analyses using direct and indirect evidence suggest individual opioids are similarly ineffective (low to very low certainty evidence). - There are insufficient data to draw conclusions about efficacy in different chronic pain conditions. - There was no difference in pain reduction, pain response, or function with opioids vs. non-opioids (e.g., NSAIDs, antiepileptics, antidepressants) in studies evaluating 1 to less than 6 months of treatment (moderate to high certainty evidence). Only one trial (n=231) longer than 12 months evaluated opioids vs. non-opioids, with larger reduction in pain severity with opioids vs. non-opioids. Differences were small (0.5 points on a 10-point scale) and did not meet thresholds for clinical significance. - Opioids increase risk of treatment discontinuation due to adverse events compared to both placebo and non-opioid medication. Common opioid-related adverse events included nausea, vomiting, constipation, somnolence, dizziness, and pruritus. - Observational studies also document an association between opioid use and fractures, falls, and adverse cardiovascular- and endocrine-related outcomes. Increasing opioid dose and duration of use are associated with increasing risk of overdose, opioid-related mortality, injury related to car accidents, and OUD. - While UDS, PDMP use and pill counts can identify current OUD or misuse, there is no reliable evidence that these monitoring methods will *predict subsequent* OUD or misuse. There are available screening tools to assess risk of OUD, but limited evidence on effectiveness at predicting future OUD. Measurable treatment goals should be established prior to starting treatment for chronic pain with a strategy for deprescribing if goals are not met.
Naloxone	
- Consider naloxone for people with chronic pain who are prescribed opioids and who may be at risk of an opioid overdose	- Observational studies suggest that co-prescribing naloxone with opioids is associated with 6% fewer opioid-related ED visits with each additional month since the receipt of a naloxone prescription over a one year follow-up period.
Antidepressants	
- Consider duloxetine in people with chronic pain	- Duloxetine has moderate short-term effects on pain reduction and improved physical functioning (low to moderate certainty evidence). Doses above 60 mg per day probably provide no more benefits than standard doses of 60 mg daily. - Milnacipran may reduce pain by a small amount compared to placebo (low to moderate certainty evidence). - There are no head-to-head comparisons of antidepressants for treatment of chronic pain and insufficient data to draw conclusions regarding other antidepressants. Studies of antidepressants evaluated pain improvement over 2 weeks to 9 months, and there are no clinical studies to evaluate long-term pain improvement with antidepressants. - Adverse effects are more common with antidepressants compared to placebo, and data on adverse events reported in clinical trials of people with chronic pain are limited by short study durations, poor outcome reporting, and wide confidence intervals.

Abbreviations: ED = emergency department; mg = milligrams; MME = morphine milligram equivalent; OUD = opioid use disorder; PDMP = prescription drug monitoring program; UDS = urine drug screen.

In 2022, the VA/DOD updated recommendations on use of opioids for people with chronic pain (**Table 2).**[16]

Table 2. VA/DOD recommendations for opioid use in chronic pain[16]

Topic	**Recommendation**	**Strength of Recommendation**
Initiation and Continuation	Recommend against initiation of opioid therapy for chronic non-cancer pain.	Strong against
	Recommend against long-term opioid therapy, particularly for: - younger age groups, as age is inversely associated with the risk of opioid use disorder and overdose - patients with chronic pain who have a substance use disorder.	Strong against
	For people with opioid use disorder (OUD) and co-occurring chronic pain, there is insufficient evidence to recommend any specific treatment over another between methadone, buprenorphine, or extended-release naltrexone injection.	Neither for nor against
	Buprenorphine is recommended over full opioid agonists for people who need daily opioids for chronic pain, due to lower risk of overdose and misuse. - The systematic literature review supporting this recommendation found low quality evidence that transdermal buprenorphine was equally effective at controlling pain compared to other opioids and insufficient evidence evaluating safety of buprenorphine compared to other opioids.	Weak for
	Recommend against the concurrent use of benzodiazepines and opioids for chronic pain.	Strong against
Dose and Duration	If opioids prescribed, recommend: - Lowest dose and shortest duration as indicated by patient-specific risks and benefits. - Re-evaluation of patient-specific risks and benefits (including monitoring for adverse events, OUD, and risk of overdose) when considering a dose increase. - Re-evaluation at 30 days or fewer after initiating opioid therapy with frequent follow-up visits if opioids are continued. - Against prescribing long-acting opioids for acute pain, as an as-needed medication, or when initiating long-term opioid therapy.	Strong for Strong against
Tapering	There is insufficient evidence to recommend for or against any specific tapering strategies.	Neither for nor against
	A collaborative, patient-centered approach to opioid tapering is recommended.	Weak for
Monitoring	If opioids prescribed, routine assessment and reassessment for suicide risk and self-directed violence is recommended because studies have consistently shown chronic pain is associated with increased risk of suicide.	Strong for
	Assessment for behavioral health conditions, history of traumatic brain injury, and psychologic factors (e.g., negative affect, pain catastrophizing) is recommended when considering long-term opioids; and	Strong for (chronic pain) Weak for (acute pain)

	Recommend screening for these conditions when considering opioids for acute pain as these conditions are associated with higher risk of harm with opioids.	
	If opioids prescribed, ongoing periodic reevaluation of benefits and harms based on individual risk factors is recommended. - Factors considered for this recommendation included evaluation of current standards of care based on the known risks of opioids, lack of studies to directly describe specific reassessment intervals that can improve opioid-related harms, and patient and provider burden for periodic reassessment.	Weak for
Risk Mitigation	Risk mitigation strategies recommended for people prescribed opioids: - Urine drug screening for people on long-term opioids. - Interdisciplinary care to address pain and/or behavioral health problems for people with high risk and/or aberrant behavior. - Pre-operative education to decrease the risk of prolonged opioid use for post-surgical pain.	Weak for

Prior to prescribing opioids for chronic pain, the following should be considered:[16]

- Risks do not outweigh potential functional benefits.
- Patient has a condition that is:
    - Causing severe chronic pain;
    - Interfering with function and quality of life; and
    - Failing to adequately respond to indicated non-pharmacologic and non-opioid pharmacologic therapy. Non-pharmacologic treatments for chronic pain include rehabilitation and manipulative therapies (e.g., physical therapy, occupational therapy, chiropractic medicine), interventional procedures (e.g., trigger point injections, joint injections, acupuncture), psychological and behavioral interventions (e.g., motivational interviewing, cognitive behavioral therapy), and complementary and integrative treatments (e.g., yoga, tai chi).
- Clear and measurable functional goals are established.
- Monitoring:
    - Patient is willing and able to access adequate follow-up for prescribed opioids.
    - PDMP and urine drug screen (UDS) are concordant with expectations (no aberrant behavior)
    - Patient is fully informed and consents to treatment with opioids

For people prescribed opioids, risk mitigation strategies include UDS, PDMP evaluation, overdose education, naloxone distribution, and provider-follow up with frequency determined by risk.[16]

Contraindications for initiation of opioids include evaluation of suicide risk, substance use disorder, and concomitant benzodiazepine use.[16]

In patients already prescribed opioids, evidence of OUD may include self-escalating doses, early refills, difficulty tapering, cravings, continued use despite medical or psychological consequences, and interpersonal or social problems related to opioid use.[16]
Tapering, dose reduction and discontinuation of opioids should be considered when there is:[16]

- Lack of clinically meaningful improvement in functional goals;

- Improvement in the underlying pain condition;
- Pain condition that is not effectively treated with opioids (e.g., back pain with normal MRI; fibromyalgia);
- Increased risk of overdose or adverse events (based on concomitant medications, high dose, or co-occurring medical or behavioral health disorders);
- Lack of participation in risk mitigation measures or comprehensive pain care plan; or
- Significant side effects, overdose, or diversion. Side effects could include risk of developing or worsening opioid use disorder, depression, falls, fractures, sleep disordered breathing, sedation, cognitive dysfunction, motor vehicle accidents, nausea, constipation, dry mouth, hypogonadism, immune system dysfunction, worsening or prolonged pain, and reduction in function or quality of life.

Acute and Chronic Low Back Pain:

In 2022, the VA/DOD updated recommendations for treatment of low back pain.[8] Recommendations included NSAIDs for both acute (<4 weeks) and chronic low back pain and duloxetine for low back pain lasting longer than 4 weeks (weak recommendation for treatment).[8] Recommended non-pharmacologic management included acupuncture, cognitive behavioral therapy and/or mindfulness-based stress reduction, clinician-directed exercise programs, and spinal mobilization/manipulation. They found insufficient evidence to make recommendations for or against gabapentin, pregabalin, tricyclic antidepressants, topical pain medications, or non-benzodiazepine muscle relaxants for short-term use.[8] They suggested against offering muscle relaxants or opioids for chronic low back pain, and against offering acetaminophen, monoclonal antibodies, corticosteroids, or benzodiazepines for people with acute or chronic low back pain.[8]

In 2020, NICE published recommendations for treatment of low back pain and sciatica.[7] Recommendations generally apply when there is not an identified underlying pathology (e.g., cancer, infection, trauma, or inflammatory disease). Recommendations for pharmacologic therapy include use of NSAIDs as an initial treatment option. NSAIDs are recommended at the lowest effective dose for the shortest time with appropriate monitoring and gastroprotective treatment because of potential risks related to adverse events (including gastrointestinal, liver, cardio-renal toxicity).[7] Codeine with or without acetaminophen can be considered for acute low back pain, only if an NSAID is contraindicated, not tolerated, or ineffective. NICE recommends against routinely offering codeine or other opioids for acute low back pain or for managing for managing chronic sciatica or low back pain lasting more than 3 months. The following therapies are not recommended: gabapentinoids, other antiepileptics, corticosteroids, or benzodiazepines for managing sciatica as there is no evidence of benefit and there is evidence of harm; acetaminophen alone, antidepressants, gabapentinoids, or antiepileptics for low back pain based on a lack of evidence in clinical trials for this specific type of pain. For patients already prescribed gabapentinoids, benzodiazepines, or opioids, discuss with patients about the benefits and harms of these treatments, and safe withdrawal management as part of shared decision-making process.

Chronic Neuropathic Pain:

In 2022, the American Academy of Neurology published treatment guidelines for adults with chronic painful diabetic polyneuropathy (PDN).[14] Recommendations were based on a systematic review and meta-analysis of the evidence evaluating medications by class. Standardized mean differences (SMD) of 0.2, 0.5, and 0.8 were defined for small, medium, and large effect sizes, respectively.[14] In short-term trials over 4-16 weeks, the following medication classes were more likely to improve pain compared to placebo:[14]

- SNRIs (e.g., duloxetine, venlafaxine, and desvenlafaxine): SMD 0.47; 95% CI 0.34 to 0.60; n=1884; 9 trials; moderate confidence evidence
- Gabapentinoids: SMD 0.44; 95% CI 0.25 to 0.63; n= 3,550; 16 trials; moderate confidence evidence
- Sodium channel blocker antiepileptics (e.g., carbamazepine, oxcarbazepine, lamotrigine, valproic acid, lacosamide): SMD 0.56; 95% CI 0.25 to 0.87; n=566; 5 trials; moderate certainty evidence
- SNRI-opioid dual mechanism agents (e.g., tramadol, tapentadol): SMD 0.62; 95% CI 0.38 to 0.86; n= 775; 4 trials; moderate confidence evidence
- Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine): SMD 0.95; 95% CI 0.15 to 1.75; n=139; 3 trials; low confidence evidence

- Capsaicin: SMD 0.30; 95% CI, 0.14 to 0.47; 2 trials; low confidence evidence

Recommendations for medication therapy include:[14]

- TCAs, SNRIs, gabapentinoids, and/or sodium channel blocker antiepileptics to reduce pain (Level B). Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when recommending treatment for PDN (Level B). In patients of childbearing potential with PDN, clinicians should not offer valproic acid (Level B).
- Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for PDN (Level C).
- Clinicians should offer patients a trial of a medication from a different effective class when they do not achieve meaningful improvement or if they experience significant adverse effects with the initial therapeutic class (Level B). Adequate trial was defined as titration to a therapeutic dose for about 12 weeks without clinically significant pain reduction or intolerance to side effects. For patients who achieve partial improvement with an initial therapeutic class, clinicians should offer a trial of a medication from a different effective class or combination therapy by adding a medication from a different effective class (Level B).
- Clinicians should not use opioids (Level B) or dual mechanism opioids/SNRI agents (level C) for the treatment of PDN based on limited data on efficacy with long-term use and increased risk of long-term harms. If patients are currently on opioids or dual mechanism opioids/SNRI agents for the treatment of PDN, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies (Level C).

In 2020, NICE published recommendations for treatment of neuropathic pain in adults including diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-surgical chronic neuropathic pain, and neuropathic cancer pain.[13]

For trigeminal neuralgia, offer carbamazepine as initial treatment.[13] If ineffective, refer to a pain specialist.

For neuropathic pain (except trigeminal neuralgia), medication recommendations include:[13]

- Offer amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia). If initial or subsequent treatment is not effective or tolerated, switch to another of these agents.
- Tramadol may be used only if acute rescue therapy is needed.
- Capsaicin cream may be used for people with localized neuropathic pain who wish to avoid or who cannot tolerate oral treatments.
- Do not start the following therapies for neuropathic pain without consultation from a pain specialist: antiepileptics (e.g., lacosamide, lamotrigine, valproate, levetiracetam, oxcarbazepine, topiramate), capsaicin patch, opioids (e.g., morphine, long-term use of tramadol) or venlafaxine.

Arthritis Pain

In 2022, American Academy of Orthopedic Surgeons published guidelines in adults with knee osteoarthritis.[15] Treatments included both non-pharmacologic and pharmacologic therapy; this summary focuses on medication recommendations. Pharmacologic recommendations were generally consistent with current practice and known evidence (**Table 3**). Recommendations were categorized as strong when there was high quality supporting evidence, moderate when benefits exceed potential harms but evidence is of lower quality, and limited when there is unclear balance between potential benefits and harms.[15]

Table 3. Medication recommendations for adults with knee osteoarthritis[15]

Recommendation	Strength of Recommendation
Topical NSAIDs to improve function and quality of life, when not contraindicated	Strong for
Oral NSAIDs to improve pain and function, when not contraindicated	Strong for

Oral acetaminophen to improve pain and function	Strong for
Opioids, including tramadol, are NOT recommended because they increase adverse events and are not effective at improving pain or function for knee osteoarthritis	Strong against
Intra-articular corticosteroids for short-term pain relief (up to 3 months) for symptomatic osteoarthritis of the knee	Moderate for
Oral supplements including turmeric, ginger extract, glucosamine, chondroitin, and vitamin D to reduce pain and improve function in mild to moderate knee osteoarthritis; however, evidence of efficacy is inconsistent and is very low quality	Limited

Deprescribing opioids

In 2022, the National Health and Medical Research Council of Australia published high-quality guidelines for best practices around opioid deprescribing.[19] In many cases, authors identified insufficient evidence in the literature to support recommendations for deprescribing opioids. Recommendations for which there is available evidence are outlined in **Table 4**.[19] Recommendations were categorized as recommendations that would apply to most or all individuals, conditional recommendations where not all individuals would be served by the recommended action and there need to consider individual patient circumstances, or consensus recommendations based on expert opinion.

Available evidence indicates that patient-prescriber agreements may reduce or mitigate opioid misuse, and there is insufficient evidence to determine if implementation of a deprescribing plan when initiating an opioid reduces opioid-related harms.[19] There is evidence that voluntary deprescribing of opioids does not significantly change pain or function (low certainty evidence), and may improve quality of life (very low certainty evidence).[19] After opioid deprescribing, there were greater improvements in pain intensity for people taking high dose opioids compared to lower dose opioids.[19] Patients who participated in a multidisciplinary or multimodal care model also had greater improvements in pain compared to patients who had less intensive co-interventions.[19] Patients with less intensive co-interventions were more likely to have pain and function that was unchanged after deprescribing.[19] There is evidence that involuntary deprescribing or tapering may increase risk of substance use, emotional dysregulation, opioid overdose, and suicide.[19] There is insufficient evidence to determine which specific tapering plans are associated with greater success of opioid deprescribing.[19] Many studies did not adequately report tapering approaches, others designed tapering to the individual patient needs, and most studies did not evaluate patients who were unsuccessful completing a taper.[19] The guideline also evaluated evidence of benefits and harms for opioid prescribing and deprescribing in specific populations.

- There is limited evidence to support efficacy and safety of long-term opioid use in cancer survivors (e.g., beyond the acute diagnosis and treatment phase).[19] However, adverse effects have been documented with long-term opioid use including similar rates for opioid misuse when compared to individuals without cancer.[19]
- For people with breathing disorders or who are prescribed concomitant sedating drugs that may increase the risk of opioid-related harms, there is a lack of data for efficacy of opioids, and evidence that opioid prescribing increases risk of opioid-related harms.[19]
- In people nearing the end of life, there is insufficient evidence to evaluate benefits or risk of opioid deprescribing.[19]
- In people with severe opioid use disorders, there is moderate quality evidence that deprescribing alone, without access to long-term substance use disorder treatment and care, is associated with increased risk of overdose and death.[19]

Table 4. Recommendations for Opioid Deprescribing[19]

Recommendation	Classification of Recommendation	Evidence Certainty

We suggest initiating deprescribing for people taking opioids for chronic non-cancer pain if (any of the following): • there is a lack of overall and clinically meaningful improvement from baseline in function, quality of life, or pain; • there is a lack of progress towards meeting agreed therapeutic goals; or • the person is experiencing serious or intolerable opioid-related adverse effects in the physical, psychological or social domains.	Conditional recommendation for (non-cancer pain)	Very low
We suggest avoiding opioid deprescribing for people taking opioids with severe OUD and suggest that evidence-based care, such as transition to, or referral for, medication-assisted treatment of opioid use disorder is provided.	Conditional recommendation against	Moderate
We recommend gradual tapering of opioids. Abrupt cessation of opioids without prior dose reduction may increase risks of harm.	Recommendation for	Low
We recommend tailoring the deprescribing plan based on the person's clinical characteristics, goals, and preferences.	Recommendation for	Very low
When available, we suggest the use of interdisciplinary or multidisciplinary care, or a multimodal approach that emphasizes non-pharmacological and self-management strategies to deprescribe opioids.	Conditional recommendation for	Low
We suggest the consideration of evidence-based co-interventions to support opioid deprescribing.	Conditional recommendation for	Very low

Spasticity and Pain Related to Multiple Sclerosis

In 2022, NICE updated guidelines related to spasticity associated with MS including involuntary muscle movements, muscle stiffness, pain and restriction with certain movement or positions that cause functional impairment, or changes in mobility and upper limb function.[17] Baclofen is recommended as an initial treatment option for people who have spasticity and specific treatment goals such as improving mobility or pain.[17] Prescribers should take into account contraindications, comorbid symptoms, and patient preferences as muscle relaxants may also worsen MS-related symptoms including balance and mobility.[17] Gabapentin is recommended as a second-line option if baclofen is not tolerated or does not provide adequate relief.[17] Combination therapy with baclofen and gabapentin can be considered if either medication does not provide adequate relief with maximum doses or if adverse effects prevent dose escalation.[17]

After review, 14 guidelines were excluded due to poor quality.

New Formulations or Indications:

New formulations approved by the FDA in the oral muscle relaxants PDL class include:

- Baclofen oral solution (Ozobax DS®), oral suspension (Fleqsuvy®), and oral granules (Lyvispah®) for treatment of spasticity related to multiple sclerosis and in patients with spinal cord injuries.[28-30]
- Cyclobenzaprine orally disintegrating tablets (Tonmya®) for the treatment of fibromyalgia in adults.[31]
- Methocarbamol oral suspension (Atmeksi®) indicated as an adjunct therapy to rest, physical therapy and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions in patients 16 and older.[32]
- Tizanidine oral solution (Ontralfy™) indicated for treatment of spasticity in adults.[33]

New formulations approved by the FDA in the oral NSAID PDL class include:

- Oxaprozin capsules (Coxanto®) for treatment of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis.[34] Oxaproxin was previously available as tablets.

- Celecoxib oral suspension (Vyscoxa®) for treatment of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis.[35]
- Acetaminophen/ibuprofen 325/97.5 mg oral tablets (Combogesic®) for short-term management of mild to moderate acute pain in adults.[36] Acetaminophen/ibuprofen was previously available in different dosage strengths and forms.

New formulations approved by the FDA in the opioid PDL classes include:

- Tramadol oral solution (Qdolo®) for management of pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[37]
- Tramadol/celecoxib (Seglentis®) tablets, a new combination product for management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[38]

New expanded indications approved by the FDA for any analgesic products include:

- Diclofenac (Zipsor®) capsules for pediatric patients over 12 years of age.[39] Approval was based on studies of evaluating efficacy in adults and pharmacokinetic and safety data in patients 12 to 17 years of age.[39]
- Tapentadol (Nucyenta®) for pediatric patients over 6 years of age who weigh at least 40 kg.[40] Tapentadol was previously approved in adults, and expanded use in pediatric patient was based on a study of 175 patients from 2 to 17 years who underwent surgery expected to cause moderate to severe pain, and were treated with tapentadol oral solution or placebo.[40] Analysis of supplemental opioid use by age showed that patients 6 to 17 years who received placebo had more supplemental opioid analgesic medication used within the 24 hours post-surgery compared to patients prescribed tapentadol.[40] In patients 2 to 6 years of age, supplemental opioid use was numerically greater in the tapentadol group indicating lack of efficacy for very young patients.[40]
- Capsaicin patch (Qutenza®) for treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet.[41] Capsaicin patch was previously approved for postherpetic neuralgia. Patches are provider administered and applied for 30 minutes to the feet every 3 months for diabetic peripheral neuropathy.[41] Approval was based on one 12 week, double-blind, placebo controlled, RCT which evaluated pain intensity over 12 weeks. Average pain intensity at baseline was 6.5 (on a 0-10 numeric rating scale), and almost half (47%) of patients were prescribed concomitant treatment with antiepileptics, SNRIs, or TCAs.[41] Pain intensity improved by an average of 1.92 points for people prescribed capsaicin compared to 1.37 points for placebo (LSMD -0.56; 95% CI -0.98 to -0.14) a difference which is unlikely to be clinically significant.[41]

New FDA Safety Alerts:

Table 5. Description of new FDA Safety Alerts.[42]

Generic Name	Brand Name	Month / Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
NSAIDs	Multiple	April 2021 November 2024	Warnings/Precautions	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as celecoxib. NSAIDs have been associated with serious skin reactions including fixed drug eruption which may present as a more severe variant known as generalized bullous fixed drug eruption.

Opioids	Multiple	December 2023 December 2025	Box Warning Warnings/Precautions	Extensive changes to box warning for various opioids related to risk of addiction, abuse, misuse, and respiratory depression including risk mitigation with naloxone for emergency treatment of opioid overdose. Addition of gabapentinoids as a CNS depressant which may increase risk of sedation, respiratory depression, and death with concomitant opioid use. Risks of gastrointestinal complications: opioid-induced esophageal dysfunction has been reported in patients taking opioids.
Opioids	Multiple	December 2023	Warnings/Precautions	Opioid-Induced Hyperalgesia and Allodynia: opioids can paradoxically cause an increase in pain, or an increase in sensitivity to pain. Carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety).
Methadone Tramadol	Methadose® Conzip® Qdolo® Ultram®	December 2023 September 2021	Warnings/precautions	Methadone- and tramadol-associated hypoglycemia have been reported. In most cases, patients had predisposing risk factors such as diabetes; risk may be dose dependent.
Tramadol	Conzip® Qdolo® Ultram®	September 2021	Warnings/precautions	Hyponatremia has been reported with tramadol, and many cases are severe (sodium level <120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Monitoring is recommended.
Capsaicin	Qutenza®	July 2024	Warnings/Precautions	Severe Application Site Burns: Cases of full-thickness (third-degree) and deep partial-thickness (second-degree) burns have been reported some of which have required hospitalization and skin grafting in patients who received therapy for unapproved indications and/or frequency of dosing at an application site where there had been prior skin trauma.

Randomized Controlled Trials:

A total of 284 citations were manually reviewed from the initial literature search. After further review, all except 2 citations were excluded because of wrong study design (e.g., observational), setting (e.g., inpatient or single doses in emergency settings), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or lack of applicability to a US population (e.g. based on intervention or population). Full abstracts are included in **Appendix 2**.

Table 6. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations

Khankhel, et al. 2024.[43] DB, MC, PC, RCT N=198 United States	1. Ibuprofen 400mg + topical placebo gel 2. Diclofenac 1% topical gel + oral placebo 3. Ibuprofen 400 mg + diclofenac 1% topical gel	Adults visiting the emergency department with new onset (within 2 weeks), acute, nontraumatic, nonradicular, musculoskeletal low back pain and functional impairment (RMDQ score >5)	Change in RMDQ (24-point scale evaluating function) after 2 days. A difference of 5 points was predefined as a MCID on the RMDQ.	<u>Change in RMDQ at 2 Days</u> Ibuprofen: 10.0; (95% CI 7.5 to 12.7) Diclofenac: 6.4; (95% CI 4.0 to 8.8) Combination: 8.7 (95% CI 6.3 to 11.1) Ibuprofen vs. diclofenac: MD 3.7 (95% CI 0.2 to 7.2) Ibuprofen vs. Combination: NS Diclofenac vs. Combination: NS <u>Change in RMDQ at 7 days</u> No differences between groups	There were no clinically significant differences in function between people given oral ibuprofen, topical diclofenac, or combination treatment for acute low back pain at 2 or 7 days. Baseline median RMDQ score was 19, 17, and 19 in the 3 groups, respectively. Of the 3083 patients screened, most (n=1837) were excluded because duration of low back pain was > 2 weeks or more frequent than once per month.
Tan, et al. 2026.[6] MC, OL, PG, RCT N=3908 New Zealand	1. APAP 15 mg/kg PO Q6h at age < 1 month and Q4h at age ≥ 1 month 2. Ibuprofen 5 mg/kg PO Q6h at age < 3 months or 10 mg/kg Q6h at age ≥ 3 months Administered as needed for fever or pain during the first year of life	Infants younger than 8 weeks	1. Eczema in the first year of life (defined based on UK diagnostic criteria via parent questionnaire or eczema hospitalization) OR 2. Hospitalization for bronchiolitis (e.g., bronchiolitis, viral-induced wheeze, or asthma) in the first year of life	Eczema in the first year of life 1. 322 (16.2%) 2. 296 (15.4%) absolute risk difference 0·8% (95% CI –1.5 to 3.1); p=0.48 Bronchiolitis hospitalization in the first year of life 1. 98 (4.9%) 2. 82 (4.3%) absolute risk difference 0.7% (95% CI –0.6 to 2.0); p=0.32	In infants who use ibuprofen or acetaminophen as needed for acute treatment of fever or pain during the first year of life, there is no difference in the incidence of eczema or bronchiolitis at 1 year. Infants were enrolled before 8 weeks of age and parents were supplied with the study drug. Parents completed questionnaires at 1, 3, 6, 9, and 12 months to report medication use, symptoms, hospital admissions, and exposure to comorbid conditions or confounding environmental factors. Data related to hospitalizations was collected from government health datasets. 97% of infants had at least one dose of acetaminophen; median doses: 16 89% had at least one dose of ibuprofen; median doses: 10

Abbreviations: APAP = acetaminophen; CI = confidence interval; DB = double-blind; h = hours; MC = multicenter; MCID = minimum clinically important difference; MD = mean difference; NS = not significant OL = open label; PC = placebo controlled; PG = parallel group; PO = oral; Q = every; RCT = randomized clinical trial; RMDQ = Roland Morris

Disability Questionnaire which is a 24-item scale that evaluates pain-related disability and impact on quality of life; scores range from 0-24 with higher scores indicating more impact on function.

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Appendix 1: Current Preferred Drug List

Non-steroidal anti-inflammatories, Oral

Generic	Brand	Form	PDL
celecoxib	CELEBREX	CAPSULE	Y
celecoxib	CELECOXIB	CAPSULE	Y
diclofenac potassium	DICLOFENAC POTASSIUM	TABLET	Y
diclofenac sodium	DICLOFENAC SODIUM	TABLET DR	Y
etodolac	ETODOLAC	TABLET	Y
ibuprofen	IBUPROFEN	CAPSULE	Y
ibuprofen	INFANTS' IBUPROFEN	DROPS SUSP	Y
ibuprofen	INFANT'S IBUPROFEN	DROPS SUSP	Y
ibuprofen	CHILDREN'S IBUPROFEN	ORAL SUSP	Y
ibuprofen	IBUPROFEN	ORAL SUSP	Y
ibuprofen	IBUPROFEN	TAB CHEW	Y
ibuprofen	IBUPROFEN IB	TAB CHEW	Y
ibuprofen	IBU	TABLET	Y
ibuprofen	IBU-200	TABLET	Y
ibuprofen	IBUPROFEN	TABLET	Y
ibuprofen	IBUPROFEN IB	TABLET	Y
ibuprofen	IBUPROHM	TABLET	Y
ibuprofen	MOTRIN IB	TABLET	Y
ibuprofen	PAIN RELIEF	TABLET	Y
indomethacin	INDOMETHACIN	CAPSULE	Y
ketoprofen	KETOPROFEN	CAPSULE	Y
meloxicam	MELOXICAM	TABLET	Y
nabumetone	NABUMETONE	TABLET	Y
naproxen	NAPROXEN	TABLET	Y
naproxen	NAPROXEN	TABLET DR	Y
naproxen sodium	ALL DAY PAIN RELIEF	TABLET	Y
naproxen sodium	ALL DAY RELIEF	TABLET	Y
naproxen sodium	NAPROXEN SODIUM	TABLET	Y
oxaprozin	DAYPRO	TABLET	Y
oxaprozin	OXAPROZIN	TABLET	Y
salsalate	SALSALATE	TABLET	Y
sulindac	SULINDAC	TABLET	Y
celecoxib	VYSCOXA	ORAL SUSP	N
diclofenac potassium	DICLOFENAC POTASSIUM	CAPSULE	N
diclofenac potassium	DICLOFENAC POTASSIUM	POWD PACK	N
diclofenac potassium	DICLOFENAC POTASSIUM	TABLET	N
diclofenac potassium	LOFENA	TABLET	N

diclofenac sodium	DICLOFENAC SODIUM ER	TAB ER 24H	N
diclofenac sodium/misoprostol	ARTHROTEC 50	TAB IR DR	N
diclofenac sodium/misoprostol	ARTHROTEC 75	TAB IR DR	N
diclofenac sodium/misoprostol	DICLOFENAC SODIUM-MISOPROSTOL	TAB IR DR	N
diflunisal	DIFLUNISAL	TABLET	N
diflunisal	DOLOBID	TABLET	N
etodolac	ETODOLAC	CAPSULE	N
etodolac	ETODOLAC ER	TAB ER 24H	N
fenoprofen calcium	FENOPROFEN CALCIUM	CAPSULE	N
fenoprofen calcium	NALFON	CAPSULE	N
fenoprofen calcium	FENOPROFEN CALCIUM	TABLET	N
fenoprofen calcium	NALFON	TABLET	N
flurbiprofen	ANSAID	TABLET	N
flurbiprofen	FLURBIPROFEN	TABLET	N
flurbiprofen	LURBIRO	TABLET	N
ibuprofen/famotidine	IBUPROFEN-FAMOTIDINE	TABLET	N
indomethacin	INDOMETHACIN ER	CAPSULE ER	N
indomethacin	INDOMETHACIN	ORAL SUSP	N
ketoprofen	KETOPROFEN	CAP24H PEL	N
ketorolac tromethamine	KETOROLAC TROMETHAMINE	TABLET	N
meclofenamate sodium	MECLOFENAMATE SODIUM	CAPSULE	N
mefenamic acid	MEFENAMIC ACID	CAPSULE	N
meloxicam, submicronized	MELOXICAM	CAPSULE	N
nabumetone	RELAFEN DS	TABLET	N
naproxen	NAPROSYN	ORAL SUSP	N
naproxen	NAPROXEN	ORAL SUSP	N
naproxen sodium	NAPROXEN SODIUM	CAPSULE	N
naproxen sodium	NAPRELAN	TBMP 24HR	N
naproxen sodium	NAPROXEN SODIUM CR	TBMP 24HR	N
naproxen sodium	NAPROXEN SODIUM ER	TBMP 24HR	N
naproxen/esomeprazole mag	NAPROXEN-ESOMEPRAZOLE MAG	TAB IR DR	N
oxaprozin	COXANTO	CAPSULE	N
oxaprozin	OXAPROZIN	CAPSULE	N
piroxicam	PIROXICAM	CAPSULE	N
tolmetin sodium	TOLMETIN SODIUM	CAPSULE	N
tolmetin sodium	TOLECTIN 600	TABLET	N
tolmetin sodium	TOLMETIN SODIUM	TABLET	N
diflunisal	DOLOBID	TABLET	
fenoprofen calcium	FENOPRON	CAPSULE	
ketoprofen	ORUDIS	CAPSULE	

Topical Pain Medications

Generic	Brand	Form	PDL
capsaicin	ARTHRITIS PAIN RELIEVING	CREAM (G)	Y
capsaicin	CAPSAICIN	CREAM (G)	Y
capsaicin	CAPSAICIN-HP	CREAM (G)	Y
diclofenac sodium	ARTHRITIS PAIN	GEL (GRAM)	Y
diclofenac sodium	ARTHRITIS PAIN RELIEVER	GEL (GRAM)	Y
diclofenac sodium	DICLOFENAC SODIUM	GEL (GRAM)	Y
lidocaine HCl	DERMACINRX LIDOCAINE	CREAM (G)	Y
lidocaine HCl	LIDOCAINE HCL	CREAM (G)	Y
lidocaine HCl	GLYDO	JEL/PF APP	Y
lidocaine HCl	LIDOCAINE HCL	JEL/PF APP	Y
lidocaine HCl	LIDOCAINE HCL	SOLUTION	Y
lidocaine HCl	LIDOCAINE HCL	SOLUTION	Y
lidocaine HCl	LIDOCAINE HCL VISCOUS	SOLUTION	Y
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	CREAM (G)	Y
capsaicin	CAPSAICIN	ADH. PATCH	N
capsaicin	CAPSAICIN HEAT PATCH	ADH. PATCH	N
capsaicin	CAPSIMIDE	ADH. PATCH	N
capsaicin	CAPSAICIN	LOTION	N
capsaicin/me-salicylate/menth	MEDROX	ADH. PATCH	N
capsaicin/me-salicylate/menth	MEDROX	OINT. (G)	N
capsaicin/skin cleanser	QUTENZA	KIT	N
diclofenac epolamine	DICLOFENAC EPOLAMINE	PATCH TD12	N
diclofenac sodium	DICLOFENAC SODIUM	DROPS	N
diclofenac sodium	DICLOFENAC SODIUM	SOL MD PMP	N
diclofenac sodium	PENNSAID	SOLN PK(G)	N
diclofenac/kinesiology tape	LIXOFEN	KIT	N
diclofenac/menthol/camphor	DICLOGEN	KIT	N
hydrocortisone/pramoxine	EPIFOAM	FOAM	N
lidocaine	DERMACINRX LIDOCAN	ADH. PATCH	N
lidocaine	LIDOCAINE	ADH. PATCH	N
lidocaine	LIDOCAN II	ADH. PATCH	N
lidocaine	LIDOCAN III	ADH. PATCH	N
lidocaine	LIDOCAN IV	ADH. PATCH	N
lidocaine	LIDOCAN V	ADH. PATCH	N
lidocaine	LIDODERM	ADH. PATCH	N
lidocaine	TRIDACAINE II	ADH. PATCH	N
lidocaine	TRIDACAINE III	ADH. PATCH	N
lidocaine	TRIDACAINE XL	ADH. PATCH	N

lidocaine	ZTLIDO	ADH. PATCH	N
lidocaine	LIDOCAINE	OINT. (G)	N
lidocaine HCl	LIDAFLEX	ADH. PATCH	N
lidocaine HCl	LIDOTRAL	CREAM (G)	N
lidocaine HCl	DERMACINRX LIDOEASE	GEL (GRAM)	N
lidocaine HCl	DERMACINRX LIDOGEL	GEL (GRAM)	N
lidocaine HCl	DERMACINRX LIDOREX	GEL (GRAM)	N
lidocaine HCl	TRILOGEL	GEL (GRAM)	N
lidocaine HCl	LIDOCAINE HCL	JELLY(ML)	N
lidocaine HCl	DOLOGESIC PAIN RELIEF	LIQD ROLON	N
lidocaine HCl	LIDOCAINE	LIQD ROLON	N
lidocaine/hydrocortisone ac	LIDOCAINE-HYDROCORTISONE	CREAM (G)	N
lidocaine/hydrocortisone ac	LIDOCORT	CREAM (G)	N
lidocaine/kinesiology tape	XYLIDERM	KIT	N
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	KIT	N
lidocaine HCl	LIDOCAINE HCL	CREAM (G)	
lidocaine HCl	BURN RELIEF	GEL (GRAM)	

Opioids, long-acting

Generic	Brand	Form	PDL
fentanyl	FENTANYL	PATCH TD72	Y
morphine sulfate	MORPHINE SULFATE ER	TABLET ER	Y
morphine sulfate	MS CONTIN	TABLET ER	Y
buprenorphine	BUPRENORPHINE	PATCH TDWK	N
buprenorphine	BUTRANS	PATCH TDWK	N
buprenorphine HCl	BELBUCA	FILM	N
fentanyl	FENTANYL	PATCH TD72	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	CAP ER 12H	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	TAB ER 24H	N
hydrocodone bitartrate	HYSINGLA ER	TAB ER 24H	N
hydromorphone HCl	HYDROMORPHONE ER	TAB ER 24H	N
levorphanol tartrate	LEVORPHANOL TARTRATE	TABLET	N
methadone HCl	METHADONE HCL	ORAL CONC	N
methadone HCl	METHADONE INTENSOL	ORAL CONC	N
methadone HCl	METHADOSE	ORAL CONC	N
methadone HCl	METHADONE HCL	SOLUTION	N
methadone HCl	METHADONE HCL	TABLET	N
methadone HCl	METHADONE HCL	TABLET SOL	N
methadone HCl	METHADOSE	TABLET SOL	N
morphine sulfate	MORPHINE SULFATE ER	CAP ER PEL	N

morphine sulfate	MORPHINE SULFATE ER	CPMP 24HR	N
oxycodone HCl	OXYCODONE HCL ER	TAB ER 12H	N
oxycodone HCl	OXYCONTIN	TAB ER 12H	N
oxymorphone HCl	OXYMORPHONE HCL ER	TAB ER 12H	N
tramadol HCl	CONZIP	CPBP 17-83	N
tramadol HCl	TRAMADOL HCL ER	CPBP 17-83	N
tramadol HCl	CONZIP	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	TAB ER 24H	N
tramadol HCl	TRAMADOL HCL ER	TBMP 24HR	N
levorphanol tartrate	XYVONA	TABLET	

Opioids, short-acting

Generic	Brand	Form	PDL
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	ELIXIR	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	SOLUTION	Y
acetaminophen with codeine	ACETAMINOPHEN W/CODEINE	TABLET	Y
acetaminophen with codeine	ACETAMINOPHEN-CODEINE	TABLET	Y
butorphanol tartrate	BUTORPHANOL TARTRATE	SPRAY	Y
codeine sulfate	CODEINE SULFATE	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	SOLUTION	Y
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE/ACETAMINOPHEN	TABLET	Y
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	TABLET	Y
hydromorphone HCl	HYDROMORPHONE HCL	SUPP.RECT	Y
hydromorphone HCl	DILAUDID	TABLET	Y
hydromorphone HCl	HYDROMORPHONE HCL	TABLET	Y
morphine sulfate	MORPHINE SULFATE	SOLUTION	Y
morphine sulfate	MORPHINE SULFATE	SUPP.RECT	Y
morphine sulfate	MORPHINE SULFATE	TABLET	Y
opium/belladonna alkaloids	BELLADONNA & OPIUM	SUPP.RECT	Y
opium/belladonna alkaloids	BELLADONNA-OPIUM	SUPP.RECT	Y
oxycodone HCl	OXYCODONE HCL	SOLUTION	Y
oxycodone HCl	OXYCODONE HCL	TABLET	Y
oxycodone HCl	ROXICODONE	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	CAPSULE	Y
oxycodone HCl/acetaminophen	ENDOCET	TABLET	Y
oxycodone HCl/acetaminophen	NALOCET	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE HCL-ACETAMINOPHEN	TABLET	Y

oxycodone HCl/acetaminophen	OXYCODONE W/ACETAMINOPHEN	TABLET	Y
oxycodone HCl/acetaminophen	OXYCODONE-ACETAMINOPHEN	TABLET	Y
oxycodone HCl/acetaminophen	PERCOCET	TABLET	Y
tramadol HCl	TRAMADOL HCL	TABLET	Y
acetaminophen/caff/dihydrocod	ACETAMIN-CAFF-DIHYDROCODEINE	CAPSULE	N
aspirin/codeine phosphate	ASPIRIN W/CODEINE	TABLET	N
butalbit/acetamin/caff/codeine	BUTALB-ACETAMINOPH-CAFF-CODEIN	CAPSULE	N
butalbit/acetamin/caff/codeine	FIORICET WITH CODEINE	CAPSULE	N
codeine/butalbital/ASA/caffein	ASA-BUTALB-CAFFEINE-CODEINE	CAPSULE	N
codeine/butalbital/ASA/caffein	ASCOMP WITH CODEINE	CAPSULE	N
fentanyl citrate	FENTANYL CITRATE	LOZENGE HD	N
fentanyl citrate	FENTANYL CITRATE	TABLET EFF	N
hydrocodone/acetaminophen	HYDROCODONE W/ACETAMINOPHEN	ELIXIR	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	SOLUTION	N
hydrocodone/acetaminophen	HYDROCODONE-ACETAMINOPHEN	TABLET	N
hydrocodone/acetaminophen	VERDROCET	TABLET	N
hydrocodone/ibuprofen	HYDROCODONE-IBUPROFEN	TABLET	N
hydromorphone HCl	DILAUDID	LIQUID	N
hydromorphone HCl	HYDROMORPHONE HCL	LIQUID	N
meperidine HCl	MEPERIDINE HCL	SOLUTION	N
meperidine HCl	MEPERIDINE HCL	TABLET	N
morphine sulfate	MORPHINE SULFATE	SYRINGE	N
oxycodone HCl	OXYCODONE HCL	CAPSULE	N
oxycodone HCl	OXYCODONE HCL	ORAL CONC	N
oxycodone HCl	ROXYBOND	TABLET ORL	N
oxycodone HCl/acetaminophen	PROLATE	SOLUTION	N
oxycodone HCl/acetaminophen	PROLATE	TABLET	N
oxycodone HCl/acetaminophen	ROXICET	TABLET	N
oxymorphone HCl	NUMORPHAN	SUPP.RECT	N
oxymorphone HCl	OXYMORPHONE HCL	TABLET	N
pentazocine HCl/naloxone HCl	PENTAZOCINE-NALOXONE HCL	TABLET	N
propoxyphene nap/acetaminophen	PROPOXYPHENE NAPSYLATE W/APAP	TABLET	N
tramadol HCl	TRAMADOL HCL	SOLUTION	N
tramadol HCl	TRAMADOL HCL	TABLET	N
tramadol HCl/acetaminophen	TRAMADOL HCL-ACETAMINOPHEN	TABLET	N

Muscle Relaxants, Oral

Generic	Brand	Form	PDL
baclofen	BACLOFEN	TABLET	Y
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL	TABLET	Y

methocarbamol	METHOCARBAMOL	TABLET	Y
tizanidine HCl	TIZANIDINE HCL	TABLET	Y
tizanidine HCl	ZANAFLEX	TABLET	Y
baclofen	LYVISPAH	GRAN PACK	N
baclofen	BACLOFEN	ORAL SUSP	N
baclofen	FLEQSUVY	ORAL SUSP	N
baclofen	BACLOFEN	SOLUTION	N
baclofen	OZOBAX	SOLUTION	N
baclofen	OZOBAX DS	SOLUTION	N
baclofen	BACLOFEN	TABLET	N
carisoprodol	CARISOPRODOL	TABLET	N
carisoprodol	SOMA	TABLET	N
chlorzoxazone	CHLORZOXAZONE	TABLET	N
chlorzoxazone	LORZONE	TABLET	N
cyclobenzaprine HCl	AMRIX	CAP ER 24H	N
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL ER	CAP ER 24H	N
cyclobenzaprine HCl	CYCLOBENZAPRINE HCL	TABLET	N
cyclobenzaprine HCl	FEXMID	TABLET	N
dantrolene sodium	DANTRIUM	CAPSULE	N
dantrolene sodium	DANTROLENE SODIUM	CAPSULE	N
metaxalone	METAXALONE	TABLET	N
methocarbamol	METHOCARBAMOL	TABLET	N
methocarbamol	TANLOR	TABLET	N
orphenadrine citrate	ORPHENADRINE CITRATE ER	TABLET ER	N
orphenadrine/aspirin/caffeine	NORGESIC	TABLET	N
orphenadrine/aspirin/caffeine	NORGESIC FORTE	TABLET	N
orphenadrine/aspirin/caffeine	ORPHENADRINE-ASPIRIN-CAFFEINE	TABLET	N
orphenadrine/aspirin/caffeine	ORPHENGESIC	TABLET	N
orphenadrine/aspirin/caffeine	ORPHENGESIC FORTE	TABLET	N
tizanidine HCl	TIZANIDINE HCL	CAPSULE	N
tizanidine HCl	ZANAFLEX	CAPSULE	N

Appendix 2: Abstracts of Comparative Clinical Trials

Khankhel N, Friedman BW, Baer J, et al. Topical Diclofenac Versus Oral Ibuprofen Versus Diclofenac + Ibuprofen for Emergency Department Patients With Acute Low Back Pain: A Randomized Study. *Annals of emergency medicine*. 2024;83(6):542-551.

STUDY OBJECTIVE: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are useful for a variety of musculoskeletal injuries. It is not known whether topical NSAIDs should be used for patients presenting with acute nonradicular musculoskeletal low back pain.

METHODS: We conducted a randomized, placebo-controlled double-blind study in which patients 18 to 69 years of age visiting the emergency department (ED) with acute, nontraumatic, nonradicular, musculoskeletal low back pain were randomized at the time of discharge to treatment with 400 mg oral ibuprofen + placebo topical gel, 1% diclofenac topical gel + oral placebo, or 400 mg ibuprofen + 1% diclofenac topical gel. We measured outcomes using the Roland Morris Disability Questionnaire (RMDQ), a 24-item yes/no instrument about the effect of back pain on a respondent's daily activities. The primary outcome was change in RMDQ score between ED discharge and 2 days later. Medication-related adverse events were elicited by asking whether the study medications caused any new symptoms.

RESULTS: In total, 3,281 patients were screened for participation, and 198 were randomized. Overall, 36% of the population were women, the mean age was 40 years (standard deviation, 13), and the median RMDQ score at baseline was 18 (25th to 75th percentile: 13 to 22), indicating substantial low back-related functional impairment. In total, 183 (92%) participants provided primary outcome data. Two days after the ED visit, the ibuprofen + placebo group had improved by 10.1 (95% confidence interval [CI] 7.5 to 12.7), the diclofenac gel + placebo group by 6.4 (95% CI 4.0 to 8.8), and the ibuprofen + diclofenac gel by 8.7 (95% CI 6.3 to 11.1). The between-group differences were as follows: ibuprofen versus diclofenac, 3.7 (95% CI 0.2 to 7.2); ibuprofen versus both medications 1.4 (95% CI -2.1 to 4.9); and diclofenac versus both medications, 2.3 (95% CI -5.7 to 1.0). Medication-related adverse events were reported by 3/60 (5%) ibuprofen patients, 1/63 (2%) diclofenac patients, and 4/64 (6%) patients who received both.

CONCLUSION: Among patients with nontraumatic, nonradicular acute musculoskeletal low back pain discharged from an ED, topical diclofenac was probably less efficacious than oral ibuprofen. It demonstrated no additive benefit when coadministered with oral ibuprofen. Copyright © 2024 American College of Emergency Physicians.

Tan E, McKinlay CJD, Riley J, et al. Paracetamol versus ibuprofen as required for fever or pain in the first year of life and the risk of eczema and bronchiolitis at age 1 year in New Zealand (PIPPA Tamariki): a multicentre, open-label, parallel-group, superiority, randomised controlled trial. *The Lancet Child & adolescent health.* 2026;10(3):156-166.

BACKGROUND: In non-experimental studies, early-life exposure to paracetamol is associated with an increased risk of eczema and wheeze. We aimed to compare paracetamol with ibuprofen, as required for fever or pain in the first year of life, for the risk of eczema and bronchiolitis at age 1 year.,

METHODS: PIPPA Tamariki is a multicentre, open-label, two-arm, parallel-group, superiority, randomised controlled trial done at three sites in Auckland and Wellington in New Zealand. Infants younger than 8 weeks and born in New Zealand were randomly assigned (1:1) to paracetamol alone (15 mg/kg every 6 h at age <1 months and every 4 h at age >=1 months) or ibuprofen alone (5 mg/kg every 6 h at age <3 months and 10 mg/kg every 6 h at age >=3 months), received orally as required for fever or pain, until age 1 year. Dosing was based on the New Zealand Formulary for Children. Research staff used REDCap for randomisation, which was stratified by recruitment site, maternal asthma status, and multiple birth. Key outcomes were eczema as defined by the UK Diagnostic Criteria or eczema hospitalisation in the first year of life, and hospitalisation for bronchiolitis as defined by at least one hospitalisation for bronchiolitis, viral-induced wheeze, or asthma in the first year of life. Analysis was according to the intention-to-treat principle. This trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12618000303246 (active, not recruiting).

FINDINGS: Between April 18, 2018, and July 28, 2023, 3923 infants were enrolled. 15 participants withdrew, leaving 3908 infants (1985 were randomly assigned to the paracetamol group, and 1923 to the ibuprofen group) in the intention-to-treat population. Of these participants, 1914 (49.0%) were

female and 1994 (51.0%) were male; 609 (15.6%) were Maori, 607 (15.5%) were Pacific, 926 (23.7%) were Asian, and 1754 (44.9%) were New Zealand European or other. Eczema occurred in 322 (16.2%) of 1985 participants in the paracetamol group and 296 (15.4%) of 1923 participants in the ibuprofen group (absolute risk difference 0.8% [95% CI -1.5 to 3.1]; p=0.48; adjusted odds ratio [OR] 1.10 [95% CI 0.92 to 1.32]; p=0.29). Bronchiolitis occurred in 98 (4.9%) participants in the paracetamol group and 82 (4.3%) participants in the ibuprofen group (absolute risk difference 0.7% [95% CI -0.6 to 2.0]; p=0.32; adjusted OR 1.23 [95% CI 0.82 to 1.71]; p=0.21). 19 serious adverse events were reported in 17 participants (eight [0.4%] of 1985 in the paracetamol group and nine [0.5%] of 1923 in the ibuprofen group; adjusted OR 0.47 [95% CI 0.14-1.56; p=0.21]); none were attributed to trial medication.

INTERPRETATION: There was no evidence of an important difference between paracetamol and ibuprofen in the risk of eczema or bronchiolitis at age 1 year.

FUNDING: Health Research Council of New Zealand, Cure Kids New Zealand, University of Auckland.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to February 13, 2026

1	exp Analgesics/	626627
2	exp Anti-Inflammatory Agents, Non-Steroidal/	227702
3	exp Narcotics/	155480
4	exp Muscle Relaxants, Central/	45807
5	exp Lidocaine/	27028
6	exp Capsaicin/	11812
7	exp Acetaminophen/	22319
8	suzetrigine.mp.	77
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	690449
10	exp Pain/	498447
11	exp Arthritis/	322907
12	exp Bursitis/	5663
13	exp Tendinopathy/	15760
14	exp Headache Disorders/	43900
15	exp Menstruation Disturbances/	30758
16	exp Neuralgia/	27545
17	exp diabetic neuropathies/ or exp mononeuropathies/ or exp polyneuropathies/	86386
18	exp "Wounds and Injuries"/	1083327
19	exp Muscle Spasticity/	11187
20	exp Fibromyalgia/	11033
21	exp Hiccup/	1270
22	exp Malignant Hyperthermia/	3938
23	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	1978731
24	9 and 23	130045
25	limit 24 to (english language and humans and yr="2019 -Current")	23767
26	limit 25 to "systematic review"	1774

27	limit 26 to comparative study	**93**
28	limit 24 to (yr="2021 -Current" and (clinical trial, phase iii or clinical trial, phase iv or randomized controlled trial))	3295
29	limit 28 to comparative study	356
30	exp Administration, Oral/	166224
31	exp Administration, Topical/	102051
32	exp Outpatients/	24094
33	30 or 31 or 32	283391
34	28 and 33	**140**
35	26 and 33	**51**

Appendix 4: Key Inclusion Criteria

Population	People with acute or chronic pain
Intervention	Medications in Appendix 1
Comparator	Medications in Appendix 1
Outcomes	Pain intensity, function, quality of life, disability, need for additional analgesic interventions
Setting	Outpatient

Opioid Analgesics, Short-acting

Goals:

- Restrict use of short-acting opioid analgesics for acute conditions funded by the OHP.
- Encourage appropriate monitoring, risk mitigation, and concomitant therapy for chronic pain.
- Promote use of preferred short-acting opioid analgesics.
- ~~Allow case-by-case review for members covered under the EPSDT program.~~

Length of Authorization:

- Initial: 7 to 30 days (except 12 months for end-of-life, sickle cell disease, severe burn injury, or cancer-related pain)
- Renewal: Up to 6 months

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/

Requires a PA:

- Non-preferred short-acting opioids and opioid combination products.
- All short-acting products prescribed for more than 14 days. Each prescription is limited to 7 days in treatment-naïve patients. Patients may fill up to 2 prescriptions every 90 days without prior authorization.
- All codeine and tramadol products for patients under 19 years of age

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain or with pain associated with sickle cell disease or severe burn injury are exempt from this PA.

Table 1. Daily Dose Threshold (90 morphine milligram equivalents per day (MME/day) of Oral Opioid Products.

Opioid	90 MME/day Dose	Notes
Benzhydrocodone	73.5 mg	
Codeine	600 mg	Codeine is not recommended for pediatric use; codeine is a prodrug of morphine and is subject to different rates of metabolism, placing certain populations at risk for overdose.
Dihydrocodeine	360 mg	
Hydrocodone bitartrate	90 mg	

Hydromorphone	22.5 mg	
Levorphanol tartrate	8 mg	
Meperidine	900 mg	Meperidine is not recommended for management of chronic pain due to potential accumulation of toxic metabolites.
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	400 mg	400 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Has the patient been prescribed any opioid analgesics (short or long-acting) for more than 6 weeks?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis funded by the OHP? Note: Currently, conditions such as fibromyalgia, TMJ, pelvic pain syndrome, neuropathy, and tension headache are not funded by the OHP.	**Yes:** Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #4 Note: Management of opioid dependence is funded by the OHP.

4. 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 #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is the requested medication a preferred agent?	**Yes:** Go to #7	**No:** Go to #6
6. Does the patient have lack of benefit, intolerance, or contraindication to at least 2 ~~Will the prescriber change to a~~ preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** ~~Inform prescriber of covered alternatives in class.~~Go to #7	**No:** ~~Go to #7~~Pass to RPh. Deny; medical appropriateness
7. Is the patient being treated for pain associated with sickle cell disease, severe burn injury or cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #8
8. Is the prescription for a product containing codeine or tramadol in a patient less than 19 years of age? Note: Cold symptoms are not funded on the prioritized list	**Yes:** Deny for medical appropriateness	**No:** Go to #9

9. Is the prescription for a short-acting fentanyl product? Note: Short-acting transmucosal fentanyl products are designed for breakthrough cancer pain only. This PA does not apply to transdermal fentanyl patches.	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #10
10. Is the opioid prescribed for pain related to migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber reviewed at least once in the past 1 month and verified that opioid prescribing is appropriate?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13

13. Within the past 6 weeks, has a 5-day trial of at least one non-opioid analgesic (e.g., NSAID, acetaminophen, and/or muscle relaxant) been tried for this indication at its maximum effective dose and found to be ineffective or are contraindicated?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Has the patient already received more than 30 days of opioid therapy for this pain condition?	**Yes:** Go to #15	No: Approve for up to 7 days not to exceed 90 MME
~~Is the opioid prescription for pain associated with a back or spine condition?~~	~~**Yes:** Go to #15~~	~~**No:** Approve for up to 30 days not to exceed 90 MME~~
15. Has the prescriber also developed a plan with the patient to stay active (home or prescribed exercise regimen) and with consideration of additional therapies such as behavioral health treatment (e.g., cognitive behavioral therapy), rehabilitative therapy (e.g., physical therapy, yoga, weight loss, massage), or interventional procedures (e.g., spinal manipulation or acupuncture)?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
~~Is this the first opioid prescription the patient has received for this pain condition?~~	~~**Yes:** Approve for up to 7 days not to exceed 90 MME~~	~~**No:** Go to #17~~
16. Can the prescriber provide documentation of sustained improvement in function of at least 30% compared to baseline with prior use of opioid analgesics (e.g., validated tools to assess function include: Oswestry, Neck Disability Index, SF-MPQ, 3-item PEG scale, and MSPQ)?	**Yes:** ~~Approve for up to 7 days not to exceed 90 MME~~Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.

17. Is there a plan to re-evaluate opioid therapy within 30 days?	**Yes:** Approve for up to 30 days	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**
3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture) AND behavioral health treatment (e.g., cognitive behavioral therapy, acceptance and commitment therapy)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny. Medical appropriateness
5. Is the patient currently prescribed an antidepressant OR is there documentation that the provider has evaluated antidepressant therapy for chronic pain in this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny. Medical appropriateness

~~4.~~6. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. *	**Yes:** Go to #8 Document tool used and score vs. baseline: _____	**No:** Go to #7
7. Is there documentation that the provider has assessed risks and benefits of tapering opioids within the past 3 months ~~indicating it is **unsafe** to initiate a taper at this time~~? Assessment should at minimum document 1) evaluation of patient concerns related to tapering, 2) factors which may contribute to increased risk of adverse events and 3) potential for pain improvement with a taper	**Yes:** Go to #~~5~~8 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #~~6~~9	**No:** Pass to RPh. Deny. Medical appropriateness
~~6.~~9. Has the patient had a urinary drug screen (UDS) within the past year to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #~~7~~10	**No:** Pass to RPh. Deny. Medical appropriateness
10. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #11	**No:** Pass to RPh. Deny. Medical appropriateness
11. Does the patient have a pain contract on file with the prescriber?	**Yes:** Go to 12	**No:** Pass to RPh. Deny. Medical appropriateness

~~7.~~12. Is the request for an increased cumulative daily dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #13	**No:** Go to #15
~~8.~~13. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
~~9.~~14. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #15	**No:** Pass to RPh; deny; medical appropriateness
~~10.~~15. Does the patient have any of the following risk factors for overdose? a. Concomitant CNS depressants (benzodiazepines, muscle relaxants, sedating antipsychotics, etc) b. Total daily opioid dose > 90 MME c. Recent urine drug screen indicating illicit or non-prescribed opioids d. Concurrent short- and long-acting opioid use e. Diagnosis of opioid use disorder	**Yes:** Approved duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=3: 2 month 1-2: 4 months	**No:** Approve for 6 months

*The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.
Citation of the original publication:
Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

- The Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for

patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:
    a. Assess for substance use disorder and transition to appropriate medication assisted treatment if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. May consider starting with a taper of ≤10% of the original dose per month and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.
11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine

Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *4/21 (AG); 2/20 (SS), 9/19 (DM), 11/16 (AG)*
Implementation: *5/1/21; 3/1/20; 10/1/19; 8/21/17*

Opioid Analgesics, Long-acting

Goals:

- Promote the well-being of OHP members and reduce risk for opioid misuse.
- Provide appropriate opioid coverage for people already prescribed chronic opioid therapy ~~OHP-funded conditions~~ when there is documented sustained improvement in pain and function and routine monitoring for opioid misuse. ~~Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk of misuse or increasing dose vs. benefit.~~
- Support appropriate risk mitigation strategies for patients on long-term opioid therapy.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

- Initial: 90 days (except 12 months for end-of-life, sickle-cell disease, severe burn, or cancer-related pain)
- Renewal: Up to 12 months

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/

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain, or pain associated with sickle cell disease or severe burn injury are exempt from this PA.

Table 1. Daily Dose Threshold (90 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes

Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	
Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

Table 2. Specific Long-acting Opioid Products Subject to Frequency Limits per FDA-approved Labeling.

Drug Product	Quantity Limit
BELBUCA	2 doses/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hr

Drug Product	Quantity Limit
HYSINGLA ER	1 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
MS CONTIN	3 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day

Drug Product	Quantity Limit
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria	
1. What is the patient's diagnosis?	Record ICD10 code

2. Is the request to initiate a long-acting opioid formulation? ~~Is the patient already established on any opioid treatment for >6 weeks (long-term, chronic treatment)?~~	**Yes:** Go to #4~~**Yes**: Go to **Renewal Criteria**~~	**No:** Go to #3.~~**No**: Go to #3~~
3. Does the request document a specific taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
~~3.~~4. Has the patient failed to have adequate benefit with daily use of short-acting opioids for at least 6 weeks? Note: long-acting opioids are not recommended as initial opioid therapy due to increased risk of death, overdose, and abuse. If trial of an opioid is necessary, short-acting opioids are recommended for initial treatment.	**Yes:** Go to #~~4~~5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend use of a short-acting product if opioids are necessary
~~4. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.~~	~~**Yes:** Go to #5~~	~~**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #5 Note: Management of opioid dependence is funded by the OHP.~~

5. Is there documentation that the patient has inadequate response, intolerance, or contraindication to all applicable pharmacologic treatments? Relevant treatments may include: Pharmacologic: topical pain medications, antidepressants, NSAIDs, acetaminophen, or muscle relaxants.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is there documentation that the treatment will be administered in conjunction with behavioral health therapy (e.g., cognitive behavioral therapy, acceptance and commitment therapy) AND non-pharmacologic modalities of pain management (e.g., physical or occupational therapy, supervised exercise, chiropractic/osteopathic manipulation, interdisciplinary rehabilitation, yoga, or acupuncture)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
~~6. Is the requested medication a preferred agent?~~	~~**Yes:** Go to #8~~	~~**No:** Go to #7~~
~~7. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.~~	~~**Yes:** Inform prescriber of covered alternatives in class.~~	~~**No:** Go to #8~~

~~8.~~7. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #~~12~~9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient had a urinary drug screen (UDS) in the past 1 year and verified absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #10~~0~~	**No:** Pass to RPh. Deny. Medical appropriateness
10. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #~~16~~11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Does the patient have a pain agreement on file with the prescriber?	**Yes:** Go to #~~17~~12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for an increased cumulative opioid dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #13	**No:** Go to #16
13. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #16	**No:** Pass to RPh; deny; medical appropriateness

~~9. Is the prescription for pain associated with migraine or other type of headache?~~ ~~Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Go to #10~~
~~10.~~16. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid prescribing)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #17~~6~~ Document tool used and score vs. baseline: _____	**No:** ~~Pass to RPh. Deny; medical appropriateness.~~ ~~Note: Management of opioid dependence is funded by the OHP.~~Go to #18
17. Is the request for a diagnosis for which opioids have not been studied or are not recommended? Examples of conditions for which *long-acting opioids* is are not recommended include fibromyalgia, TMJ, neuropathy, tension headache, migraine, and pelvic pain syndrome	**Yes:** Go to #18	**No:** Go to #19
18. Is there documentation that the provider has assessed risks and benefits of tapering opioids within the past 3 months? Assessment should at minimum document 1) evaluation of patient concerns related to tapering, 2) factors which may contribute to increased risk of adverse events and 3) potential for pain improvement with a taper	**Yes:** Go to #19 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness

~~11.~~19. Does the patient have risk factors for overdose? Risk factors may include, but are not limited to: a. Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.) b. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 c. Recent urine drug screen indicating illicit or non-prescribed opioids d. Concurrent short- and long-acting opioid use e. Diagnosis of opioid use disorder f. History of opioid overdose g. Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose without documentation of secure storage mechanisms (e.g., lockbox, etc)	**Yes:** Go to #20	**No:** Approve for 12 months
20. Has the patient been referred for management of OUD?	**Yes:** Approval for 3 months	**No:** Pass to RPh; deny; medical appropriateness
~~12. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)?~~ ~~Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~ ~~Note: Management of opioid dependence is funded by the OHP.~~	~~**No:** Go to #13~~

13. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
14. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid prescribing)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #16 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.
Has the patient had a urinary drug screen (UDS) within the past 3 months to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

Renewal Criteria	
What is the patient's diagnosis? _____	Record ICD10 code

~~Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?~~	~~**Yes**: Go to #3~~	~~**No**: Go to **Approval Criteria**~~
~~Does the request document a taper plan for the patient?~~	~~**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.~~	~~**No:** Go to #4~~
~~20. Is the diagnosis funded by the OHP?~~ ~~Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.~~	~~**Yes:** Go to #5~~	~~**No:** Go to #6~~

Does the patient have risk factors for overdose? Risk factors may include, but are not limited to: Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.) Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 Recent urine drug screen indicating illicit or non-prescribed opioids Concurrent short- and long-acting opioid use Diagnosis of opioid use disorder History of opioid overdose Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose without documentation of secure storage mechanisms (e.g., lockbox, etc)	**Yes:** Go to #6	**No:** Go to #7
Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #7 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness. May approve one time for a maximum of 1 month to allow time to document a taper plan or rationale for why a taper is unsafe at this time.

Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #8	**No:** Pass to RPh. Deny. Medical appropriateness
Has the patient had a urinary drug screen (UDS) in the past 1 year and verified absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness
21. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid use)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #11 Document tool used and score vs. baseline: _____	**No:** Go to #10
Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny. Medical appropriateness.
Is the request for an increased cumulative dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #12	**No:** Go to #15
Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

~~Is there documented rationale (e.g., new acute injury) to support the increase in dose?~~	~~**Yes:** Go to #15~~	~~**No:** Pass to RPh; deny; medical appropriateness~~
~~Has the member been prescribed or have access to naloxone?~~	~~**Yes:** Go to #16~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~Does the patient have a pain agreement on file with the prescriber?~~	~~**Yes:** Go to #17~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~Has the provider evaluated goals of treatment within the past 3 months?~~ ~~Risk factors may include, but are not limited to:~~ ~~Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.)~~ ~~Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2~~ ~~Recent urine drug screen indicating illicit or non-prescribed opioids~~ ~~Concurrent short- and long-acting opioid use~~ ~~Diagnosis of opioid use disorder~~ ~~History of opioid overdose~~ ~~Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose without documentation of secure storage mechanisms (e.g., lockbox, etc)~~	~~**Yes:** Approval duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less):~~ ~~Risk factors:~~ ~~>=1: 3 months~~ ~~0: 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Prioritized-List.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

- The Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:
    a. Assess for substance use disorder and transition to appropriate medication assisted treatment if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. May consider starting with a taper of ≤10% of the original dose per month and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.

11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.
Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

P&T Review: *2/23 (SS); 4/21(AG); 2/20 (SS), 9/19 (DM), 3/17; 11/16; 05/16*
Implementation: *4/1/23; 5/1/21; 3/1/20; 10/1/19*

Skeletal Muscle Relaxants

Goal(s):
- Promote use of preferred products
- Cover non-preferred drugs only for short-term treatment or ~~funded conditions.~~when there is documented evidence of benefit.
- Restrict carisoprodol to short-term use due to lack of long-term studies to assess safety or efficacy and high potential for abuse.

Length of Authorization:
- Up to 3 - 6 months

Requires PA:
- Non-preferred agents

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. Has the patient had inadequate benefit, intolerance, or contraindication to at least 2 preferred products? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Go to #3	**No:** Pass to RPh; Deny medical appropriateness
3. Has an opioid been prescribed within the past 30 days?	**Yes:** ~~Deny; medical appropriateness~~Go to #4	**No:** Go to #~~7~~5
4. Is there documentation that the opioid will not be prescribed in conjunction with the muscle relaxant OR is there documentation that the provider has implemented a taper and risk mitigation plan for concomitant prescribing? At minimum, a risk mitigation plan should document 1) evaluation of factors contributing to overdose risk, 2) informed consent and patient education on risk of overdose, and 3) concomitant naloxone prescribing.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is there documentation of symptom impact on function or quality of life using a validated scale?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~Is the diagnosis funded by the Oregon Health Plan?~~	~~**Yes:** Go to #4~~	~~**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP~~ ~~If eligible for EPSDT review: Go to #**3**~~
~~Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?~~	~~**Yes:** Go to #4~~	~~**No:** Pass to RPh. Deny; medical necessity.~~
~~2. Will the prescriber consider a change to preferred product?~~ ~~Message:~~ ~~• Preferred products do not require PA~~ ~~• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.~~	~~**Yes:** Inform prescriber of covered alternatives in class~~	~~**No:** Go to #5~~
~~3.~~6. Is drug requested carisoprodol?	**Yes:** Go to #~~6~~7	**No:** ~~Approve for up to 3 months~~Go to #10
~~4.~~7. Does total quantity of carisoprodol exceed 56 tablets in 90 days? From claims, document product, dose, directions, and amount used during last 90 days.	**Yes:** Go to #8	**No:** Approve for up to 3 months
~~5.~~8. Does patient have a terminal illness (e.g. metastatic cancer, end stage Parkinson's disease, ALS)?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Go to #9

Approval Criteria		

~~6.~~9. Pharmacist's statement:
 	
• Carisoprodol cannot be approved for long term usage.
• Patients are limited to 56 tablets in a 90 day period.
• It is recommended that the patient undergo a "taper" of the carisoprodol product of which a supply may be authorized for this to occur.
• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following:
  ○ >65 years of age; or
  ○ renal failure; or
  ○ hepatic failure; or
  ○ take > 1400 mg per day?
	Yes: Document reason and approve long taper:
	
	• Authorize 18 tablets
	• Reduce dose over 9 days
	• 350 mg TID X 3 days, then
	• 350 mg BID X 3 days, then
	• 350 mg daily x 3 days then evaluate
		No: Approve short taper:
		
		• Authorize 10 tablets
		• Reduce dose over 4 days
		• 350 mg TID x 1 day, then
		• 350 mg BID x 2 days, then
		• 350 mg daily x1 day, then evaluate

10. Is the request for acute treatment (<3 months duration) or intermittent use for acute symptoms? Note: Intermittent use may be validated based on claims history.	**Yes:** Approve for up to 3 months	**No:** Go to #11
11. Is the request for continuation of treatment for a patient already established on chronic therapy?	**Yes:** Go to 12	**No:** Approve for up to 3 months
12. Is there documentation of improvement in symptoms, function, or quality of life using a validated scale? The same scale used to evaluate symptoms prior to treatment should be used to assess benefit.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *9/19 (KS); 3/17 (DM); 3/17; 11/14; 9/09; 2/06; 2/04; 11/01; 2/01; 9/00; 5/00; 2/00*
Implementation: *4/1/17; 1/1/15, 1/1/14, 1/1/10, 11/18/04*

Analgesics, Non-Steroidal Anti-Inflammatory Drugs

Goal(s):

- To ensure that non-preferred oral and nasal spray NSAIDs are used for conditions funded by the OHP and support individual review for the EPSDT program.
- Restrict ketorolac to short-term use (5-day supply every 60 days) per the FDA black boxed warning.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred oral and nasal spray NSAIDs.
- Ketorolac: Maximum of one claim per 60 days, with a maximum 20 tablets/5-day supply or 126 mg/day for nasal spray (maximum 5-day combined duration of treatment every 60 days).

Preferred 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 diagnosis funded by the Oregon Health Plan?	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3.

Approval Criteria		
3. Is there documentation of medical appropriateness and medical necessity? Definitions for medical appropriateness include use for an FDA indication AND use, contraindication, or intolerance to preferred agents in the class. Medical necessity includes documentation that the diagnosis impacts the patient's health.	**Yes:** Go to #4	**No:** Pass to RPh; deny medical appropriateness or medical necessity
4. Is this a request for ketorolac, new or continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims.	**Yes:** Document prior therapy in PA record. Go to #5.	**No:** Go to #6
5. Is request for more than a 5-day supply of ketorolac within 60 days (200 mg total over 5 days for tablets, 630 mg total over 5 days for the nasal spray)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation that the patient has had inadequate benefit, intolerance, or contraindication to at least 3 ~~Will the prescriber consider switching to a~~ preferred products? Message: • Preferred products do not require PA. • Preferred products are evidence-based and reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Approve for up to 12 months~~Inform prescriber of covered alternatives in class~~.	**No:** ~~Approve for up to 12 months.~~ Pass to RPh. Deny; medical appropriateness.

P&T Review: *12/22; 2/21 (KS), 3/16 (MH); 11/14; 9/13; 2/12; 9/09; 2/06*
Implementation: *1/1/23; 1/1/15, 1/1/14, 5/14/12, 1/1/10*

Lidocaine Patch

Goal(s):

- Provide coverage only for diagnoses that are supported by the medical literature.
- Restrict use to OHP-funded diagnoses in adults. Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- 90 days to 12 months (criteria specific)

Requires PA:

- Lidocaine Patch

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 diagnosis supported by evidence for its use in that condition (refer to Table 1 for examples)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis an OHP-funded diagnosis (refer to Table 1 for examples)?	**Yes:** Go to # 5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #4.
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Approve for 90 days	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
5. Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 6
6. Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days

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

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

Condition	Lidocaine Patch
Funded	Evidence Supports Use
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	

P&T Review: *8/20 (DM); 7/18; 3/17*
Implementation: *4/1/17*

Suzetrigine (Journavx™)

Goal(s):

- Allow use in accordance with available medical evidence for safety and efficacy.

Length of Authorization:

- Up to 14 days per acute injury/surgery

Requires PA:
Suzetrigine quantities greater than 5 tablets total (50 mg tablets, a 48-hour supply) within 30 days

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 patient an adult 18 years or older?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for treatment of acute pain? Note: Acute pain is generally considered to last less than 30 days.	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the pain documented to be moderate to severe?	**Yes**: Go to #5 Record pain rating_____ using visual analogue scale (VAS), numeric pain rating scale (NPRS) or other validated measure.	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient already received 14 days of suzetrigine for this indication?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is there documentation that the patient is failing to receive adequate pain relief from, or have contraindications to, both acetaminophen and a non-steroidal anti-inflammatory agent?	**Yes:** Approved requested doses up to maximum 30 tablets (total includes any doses received before prior authorization requirement).	**No:** Pass to RPh. Deny; medical necessity.

P&T/DUR Review: 6/25 (SF)
Implementation: 8/1/25

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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New Drug Evaluation: Lynkuet® (elinzanetant), capsules

Date of Review: April 2026
Generic Name: Elinzanetant

End Date of Literature Search: 12/10/2025
Brand Name (Manufacturer): LYNKUET (Bayer)
Dossier Received: yes

Plain Language Summary:

- Menopause typically occurs between the age of 45 to 55 years in people who identify as women at birth. Menopause can result in hot flashes and night sweats which are also called vasomotor symptoms. These symptoms can be severe enough to interrupt sleep or cause anxiety and depression in some women.
- Hormone therapy with medications that contain estrogen or progesterone can be prescribed to reduce how often hot flashes occur and how severe they feel. However, estrogens when taken without progesterone can increase the risk of uterine cancers. People that have a uterus often take estrogen with progesterone to alleviate the risk of uterine cancer.
- A new medicine, LYNKUET (elinzanetant), was approved by the Food and Drug Administration (FDA) to treat hot flashes due to menopause. It is similar to fezolinetant, which has been available for a few years. These medicines are not hormone therapy. Neither medicine is a hormone, like estrogen or progesterone.
- This review looked at the evidence for how well elinzanetant works and the side effects caused by this medicine. Two studies found that the amount and the severity of hot flashes were reduced in post-menopausal women who received elinzanetant 120 mg once a day.
- Side effects reported with elinzanetant included headache, feeling tired or drowsy, dizziness, stomach pain, rash, muscle spasm, and diarrhea. It is unclear if the medicine affects the liver, so blood work should be done to check liver function tests before and once after starting treatment.
- Hormone therapy is covered by the Oregon Health Plan's fee-for-service program. Prior authorization must be submitted by the prescriber before elinzanetant can be covered.

Research Questions:

1. What is the efficacy of elinzanetant in reducing the frequency of moderate-to-severe vasomotor symptoms associated with menopause?
2. What are the harms of elinzanetant when used to reduce vasomotor symptoms associated with menopause?
3. Does elinzanetant differ in effectiveness or harms based on specific demographic characteristics (e.g., smoking status, age, race, ethnicity)?

Conclusions:

- The dual neurokinin-1 and neruokin-3 receptor antagonist LYNKUET (elinzanetant) received FDA approval October 2025 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.[1] Two, phase 3, randomized controlled trials (RCTs), OASIS 1 and OASIS 2,[2] contribute to the efficacy data for this indication and are evaluated in **Table 3.** In these identically designed trials, a total of 796 of postmenopausal patients identified as

women at birth aged 45 years to 60 years who had an average of 50 moderate to severe vasomotor symptoms per week were randomized to elinzanetant 120 mg or placebo once a day for 12 weeks.[2]

- The co-primary endpoints studied in both trials were least-square mean (LSM) change in frequency (a reduction of at least 2 vasomotor events per day is considered clinically significant) and change in severity of moderate-to-severe vasomotor symptoms at Weeks 4 and 12 (a 50% reduction in severity is considered clinically significant).[2] Frequency and severity of vasomotor symptoms was defined as mild, moderate, or severe and recorded in an electronic diary twice daily by study participants.[2] The results are summarized in **Table 1**. These two trials provide moderate-quality evidence that elinzanetant provides statistically significant reductions in vasomotor symptom frequency and severity for up to 12 weeks.[2]
- In OASIS 1 and 2, commonly reported adverse effects through the first 12 weeks of treatment included headache, fatigue, gastroesophageal disease, dizziness, nausea and somnolence.[1] Similar adverse events were reported in the 52-week Oasis 3 trial and are presented in **Table 2** below.
- Concomitant use of elinzanetant should be avoided with strong CYP3A4 inhibitors, grapefruit juice, strong CYP3A4 inducers, and moderate CYP3A4 inducers.[1] When co-administered with moderate CYP3A4 inhibitors, the dose of elinzanetant should be reduced to 60 mg once a day.[1] Based on findings from animal studies, elinzanetant may cause pregnancy loss or stillbirth.[1] For this reason, elinzanetant is contraindicated in pregnancy.[1]
- Elevations in serum transaminase (alanine transaminase [ALT] and/or aspartate aminotransferase [AST]) concentrations equal to or greater than three times the upper limit of normal (ULN) occurred in 0.6% of patients receiving elinzanetant and 0.4% of patients receiving placebo up to 12 weeks in the 3 clinical trials.[1] For this reason, the FDA labeling recommends obtaining baseline bloodwork (including ALT, AST, alkaline phosphatase, and total and direct bilirubin) prior to initiation.[1] Therapy should not be started if serum transaminase concentration is equal to or exceeds two times the upper limit of normal (ULN) or if the total bilirubin is equal to or exceeds two times the ULN.[1] Follow-up evaluations of hepatic transaminase concentrations should be performed 3 months after initiation of therapy.[1] Long-term studies will provide more data on the risks of elinzanetant-induced hepatic injury.
- Elinzanetant has been studied in women with moderate to severe vasomotor symptoms who were receiving endocrine therapy (tamoxifen or aromatase inhibitors) for hormone receptor-positive breast cancer (n = 474).[3] In this trial, elinzanetant-treated patients experienced statistically significant reductions in frequency of vasomotor symptoms compared to placebo-treated patients.[3] Use in this patient population is not yet FDA-approved.
- There is insufficient evidence to assess if elinzanetant differs in effectiveness or harms for any other patient-specific factors like smoking status, age, race, or ethnicity.

Recommendations:

- Create a PDL class called “Neurokinin Receptor Antagonists” and include both fezolinetant and elinzanetant in this class.
- Designate elinzanetant as non-preferred on the Preferred Drug List (PDL) with prior authorization (PA) criteria as presented in **Appendix 2**.

Background:

Menopause is characterized by decreased ovarian estrogen secretion with corresponding cessation of the menstrual cycle and onset of vasomotor and vulvovaginal atrophy symptoms.[4] Menopause typically occurs between the age of 45 to 55 years, with a mean age of onset around 51 years.[5] As menopause progresses, approximately 60% to 80% of women experience vasomotor symptoms; 20% of them experience severe symptoms.[6] Hot flashes and night sweats are the primary vasomotor symptoms, which may also be associated with sleep and mood disturbances, as well as decreased cognitive function.[7] Hot flash episodes usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety, and on occasion, heart palpitations.[8] Vasomotor symptoms can persist for 7 to 10 years.[5] These symptoms can have a negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.[7]

Prevalence of vasomotor symptoms varies between different racial and ethnic groups, with a higher incidence and longer duration of symptoms in Black and Hispanic women.[6] In all women, vasomotor symptoms increase as women progress from premenopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.[6] Other risk factors related to severity of vasomotor symptoms include older age, body mass index greater than 30 kg/m^2, lack of college education, smoking history longer than 40 pack-years, and high baseline anxiety or depression scores.[6]

The American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and Endocrine Society recommend systemic menopausal hormone therapy – either estrogen combined with progestogen in patients with a uterus or estrogen alone in patient without a uterus – as first-line treatment for vasomotor symptoms of menopause.[9] The NAMS recommends oral or topical estrogen in women without contraindications who need additional treatment for menopausal symptoms.[10] Contraindications to estrogen include history of uterine cancer, hepatic disease or a venous thromboembolism event (VTE).[10] In addition, women over the age of 60 years or those who are greater than 10 years from the onset of menopause should not use hormone therapy due to an unfavorable risk-to-benefit ratio.[10] In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia or carcinoma.[10]

Systemic estrogen alone or combined with a progestogen reduces the frequency of vasomotor symptoms by approximately 75% compared with placebo.[5] Vasomotor symptom reduction by 50% or greater is considered clinically meaningful.[10] In clinical trials, a reduction of at least 2 moderate to severe hot flashes per day is considered a clinically significant reduction in frequency of symptoms.[10] Estrogen therapy is FDA approved for 4 indications: treatment of moderate to severe vasomotor symptoms; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism; and treatment of moderate to severe vulvovaginal symptoms.[10]

Nonhormonal treatment options are also available to reduce vasomotor symptoms in those with contraindications to hormone therapy or who prefer not to receive hormone therapy. The 2023 NAMS position statement on nonhormonal therapy for management of menopausal symptoms recommends selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake Inhibitors (SNRIs), gabapentin, and oxybutynin for treatment of vasomotor symptoms.[9] All of the nonhormonal therapies are prescribed off-label but have evidence of efficacy at reducing severity or frequency of vasomotor symptoms, although their relative comparative evidence is insufficient.[9]

Selective neurokinin receptor antagonists are another class of nonhormonal therapies studied to relieve vasomotor symptoms. The origin of hot flashes is in the thermoregulatory center of the hypothalamus.[11] This area of the brain is innervated by kisspeptin/neurokinin B/dynorphin (KNDy) neurons.[11] The KNDy neurons are stimulated by neurokinin B, acting at the neurokinin 3 receptors, and are inhibited by estrogen.[11] When estrogen levels decline with the menopause transition, neurokinin 3 receptor-mediated activation is then unopposed in the absence of estrogen.[11] This leads to the hypertrophy of the KNDy neurons and alters the activity of the thermoregulatory center, resulting in hot flashes.[11]

Fezolinetant is a selective neurokinin 3 receptor antagonist indicated to reduce vasomotor symptoms associated with monopause.[11] Fezolinetant is also included in the NAMS position statement as an alternative to hormonal therapy for management of vasomotor symptoms (high-quality evidence).[9] The FDA has issued a black-boxed warning that fezolinetant can cause rare but serious liver injury based on a postmarketing case reports.[12]

Elinzanetant is a newly approved dual neurokinin-1 and neurokinin-3 receptor antagonist for management of vasomotor symptoms associated with menopause. It is pharmacologically similar to fezolinetant, which only inhibits neurokinin-3. The phase 3 RCTs assessed the impact of elinzanetant on the reducing the frequency and severity of hot flashes, improvements sleep disturbance and quality of life.

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of patient-centered instruments that evaluate physical, mental, and social health.[13] The validated PROMIS Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) questionnaire is a short form derived from the 27-item PROMIS SD item bank.[14] The PROMIS SD SF 8b questionnaire assesses the degree of sleep disturbance over the past 7 days, with the 8 items particularly investigating restless sleep, satisfaction with sleep, refreshing sleep, difficulties falling asleep, staying asleep, getting to sleep, amount of sleep, and sleep quality.[14] Items are scored on a 5-point Likert scale, and the 8 single item scores are summed to yield total raw scores (range, 8-40), with higher scores indicating more disturbed sleep.[13] A change of 8 points or more in the PROMIS SD-SF-8b score is considered a clinically meaningful change in sleep disturbance.[13]

The 29-item Menopause Quality of Life (MENQOL) questionnaire assesses the presence of menopausal symptoms over the previous week.[15] Participants indicate whether or not they experienced a particular symptom and rate how bothersome it was on a 7-point scale (range, 0-6, with higher scores indicating the symptom is more bothersome).[15] The 29 items assess 4 domains of symptoms and functioning: vasomotor symptoms (items 1-3), psychosocial (items 4-10), physical (items 11-26), and sexual (items 27-29) domains.[15] Responses to single items are used to calculate 29 individual item scores. The 4 domain scores are calculated as a mean of converted single-item scores (range, 1-8, with higher scores indicating a higher degree of bothersome symptoms), and the mean of the 4 domain scores yield the MENQOL total score.[15] A change of 0.9 points represents a clinical meaningful difference.[2] Although health-related quality of life assessments such as the MENQOL questionnaire are useful for assessing the benefits of new treatments on menopause-related quality of life, demonstration of a statistical difference from placebo does not necessarily mean that improvements are clinically meaningful.[16] More details regarding the safety and efficacy of elinzanetant are discussed in the clinical summary below.

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

Clinical Efficacy:
Elinzanetant received FDA approval for the treatment of moderate to severe vasomotor symptoms due to menopause.[1] The recommended dose is 120 mg (two 60 mg capsules) once daily at bedtime.[1] Two identically designed RCTs, OASIS 1 (n=396) and OASIS 2 (n=400), contribute to the short-term efficacy data for elinzanetant, which are described and evaluated in **Table 3**.

In the trials, women aged 40 to 65 years with moderate to severe menopausal vasomotor symptoms were randomized 1:1 to elinzanetant 120 mg or placebo once daily.[2] Postmenopausal status was defined as at least 12 months of spontaneous amenorrhea, or at least 6 months of spontaneous amenorrhea with serum follicle stimulating hormone levels greater than 40 mIU/mL and a serum estradiol concentration of less than 30 pg/mL, or at least 6 months after hysterectomy with serum follicle-stimulating hormone greater than 40 mIU/mL and serum estradiol less than 30 pg/mL, or at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy.[1] The study population included women with prior hysterectomy (38.8%), prior uni-/bilateral oophorectomy (20.6%), or prior menopausal hormone therapy use (31.4%).[1] For study enrollment, patients were required to have experienced at least 50 moderate to severe hot flashes per week.[1]

Participants in the elinzanetant arm received the active medication for 26 weeks, while patients in the placebo arm received placebo for 12 weeks and then switched to elinzanetant for the next 14 weeks. Co-primary end points included daily mean change in frequency and severity of vasomotor symptoms from baseline to weeks 4 and 12, as measured by an electronic hot flash diary that patients completed twice daily.[2] Possible ranges were 0 to 180 for the vasomotor symptom frequency score.[2] Mild hot flashes were defined as a sensation of heat without sweating (score of 1), moderate as a sensation of heat with sweating

but able to continue activity (score of 2), and severe as a sensation of heat with sweating that causes cessation of activity (score of 3).[2] In both trials, the week 4 and 12 endpoints also met clinically meaningful reduction in the frequency of moderate to severe hot flashes (≥2 hot flashes over 24 hours as presented in **Table 3**).[1] However, a clinically meaningful reduction with elinzanetant in the severity of vasomotor symptoms was not met. A reduction in 50% or more in the severity of vasomotor symptoms is considered a clinically meaningful effect.[10]

Secondary end points included effects on sleep disturbance (as measured by the PROMIS SD SF 8b total score) and quality of life (as measured by the MENQOL questionnaire total score) from baseline to week 12.[2] In both trials, the PROMIS SD SF 8b total score (range, 8 to 40) was converted to a total T-score to analyze this secondary endpoint (range 28.9 to 76.5).[2] A T-score of 50 represented the mean sleep disturbance score in a reference population.[2] T scores of 55 or greater, 60 or greater, and 70 or greater represented mild, moderate, and severe levels of sleep disturbances, respectively, in the reference population.[2] Both secondary endpoints showed statistically significant differences in favor of elinzanetant over placebo in the trials (**Table 3**).[17]

Trial Limitations

The OASIS 1 and 2 trials included only post-menopausal individuals.[18] Individuals experiencing vasomotor symptoms with perimenopause or due to endocrine therapy for breast cancer were not included.[18] Participants were primarily White, with 12% to 19% Black or African American and less than 10% Hispanic or Latino.[18] Other study limitations that may lead to certain biases include the subjective nature of how vasomotor symptoms present and the accuracy of recording each event, which may explain the strong placebo response in these trials.[18]

Long-Term Studies

The OASIS 3 (n=628) trial was a randomized, multi-center, multi-country, double-blind, placebo-controlled, parallel-group trial in which postmenopausal women aged 40 to 65 years were randomized 1:1 to receive either elinzanetant 120 mg daily or placebo for the full 52-week treatment period.[19] OASIS 3 was designed to provide long-term safety data at 52 weeks and supportive efficacy data at 12 weeks. Unlike the OASIS 1 and 2 trials, there was no requirement for a minimum number of vasomotor events per week. Baseline moderate to severe vasomotor event frequency was less than in OASIS 1 and 2 as women experienced a mean of 6.7 and 6.8 events per day (46 to 48 events per week) in the elinzanetant and placebo arms, respectively.[19] The primary efficacy endpoint for OASIS 3 was the mean change in the frequency of moderate to severe vasomotor symptoms as assessed by the patient-reported results in a daily hot flash diary from baseline to week 12.[19] At week 12, the LSM change from baseline in daily frequency of moderate to severe hot flashes was -5.4 for elinzanetant-treated patients and -3.5 for placebo-treated patients (difference, -1.6; 95% CI,- 2.0 to -1.1; p<0.001).[19] At baseline, the mean daily frequency of moderate to severe vasomotor symptoms was 11.4 episodes in the elinzanetant group and 11.5 episodes in the placebo–group.

In OASIS 4, women aged 18 to 70 years with moderate to severe vasomotor symptoms who were receiving endocrine therapy (tamoxifen or aromatase inhibitors) for hormone receptor-positive breast cancer (n = 474) were enrolled.[3] Patients were randomly assigned in a 2:1 ratio to receive elinzanetant 120 mg once a day for 52 weeks or placebo once daily for 12 weeks followed by elinzanetant 120 mg once a day for 40 weeks.[3] The primary end points were the LSM change in the mean daily frequency of moderate to severe vasomotor symptoms from baseline to week 4 and week 12.[3] At baseline, the mean daily frequency of moderate to severe vasomotor symptoms was 11.4 episodes in the elinzanetant group and 11.5 episodes in the placebo group.[3] At week 4, the LSM change from baseline was −6.5 episodes with elinzanetant and −3.0 episodes with placebo (difference, −3.5 episodes; 95% CI, −4.4 to −2.6; P<0.001).[3] At week 12, the LSM change was −7.8 episodes with elinzanetant and −4.2 episodes with placebo (difference, −3.4 episodes; 95% CI, −4.2 to −2.5; P<0.001).[3]

Clinical Safety:

In OASIS 1 and 2, commonly reported adverse effects through the first 12 weeks of treatment included headache, fatigue, gastroesophageal disease, dizziness, nausea and somnolence.[1] Similar adverse events were reported in the 52-week OASIS 3 trial. Ten cases of liver enzyme elevation occurred in the 52-week study, including 6 cases with elinzanetant; 5 cases were mild and one case was assessed as moderate.[19] These elevations were mostly asymptomatic and resolved in 5 of the 6 cases; the final case had an unknown outcome.[19] A summary of common adverse events reported in OASIS 3 is presented in **Table 2.**

Table 2. Adverse Events Reported in the OASIS 3 trial over 52 weeks[1]

Adverse Event	**Elinzanetant (n=313) N (%)**	**Placebo (n=314) N (%)**
Headache	30 (9.6)	22 (7.0)
Fatigue	23 (7.3)	9 (2.9)
Dizziness	19 (6.1)	6 9 (1.9)
Somnolence	16 (5.1)	4 (1.3)
Abdominal Pain	14 (4.5)	8 (2.5)
Rash	13 (4.2)	5 (1.6)
Diarrhea	12 (3.8)	3 (1.0)
Muscle Spasms	10 (3.2)	2 (0.6)

In OASIS-4 the most commonly reported adverse effects were headache, fatigue, and somnolence.[3] Serious adverse events occurred during weeks 1 through 12 in 8 participants (2.5%) receiving elinzanetant and 1 participant (0.6%) receiving placebo.[3] Elevations in liver-enzyme levels that were observed in 5 women, and all of these elevations occurred while the women were taking elinzanetant.[3] All cases were reversible and there did not appear to be a substantive hepatotoxicity signal with elinzanetant.[3]

Elinzanetant is primarily metabolized by the CYP3A4 hepatic enzyme and its metabolism can be impacted by co-administration with CYP3A4 inhibitors or inducers.[1] Concomitant use of elinzanetant should be avoided with strong CYP3A4 inhibitors, grapefruit juice, strong CYP3A4 inducers, and moderate CYP3A4 inducers.[1] When co-administered with moderate CYP3A4 inhibitors, the dose of elinzanetant should be reduced to 60 mg once a day.[1] Based on findings from animal studies, elinzanetant may cause pregnancy loss or stillbirth.[1]

Elevations in serum transaminase (ALT and/or AST) concentrations equal to or greater than three-times the ULN occurred in 0.6% of patients who received up to 12 weeks of elinzanetant and 0.4% of patients who received placebo in the OASIS 1, 2 and 3 trials.[1] For this reason, the manufacturer recommends obtaining baseline ALT, AST, alkaline phosphatase, and total and direct bilirubin prior to initiation of elinzanetant to evaluate hepatic function and risk for injury.[1] Therapy should not be started if serum transaminase concentrations are equal to or exceed 2-times the ULN or if the total bilirubin is equal to or exceeds 2 times the ULN.[1] Follow-up evaluations of hepatic transaminase concentration should be performed 3 months after initiation of therapy.[1] Elinzanetant is not recommended for use in patients with end stage renal disease with or without hemodialysis or in patients with moderate to severe hepatic impairment.[1]

Patients should be advised about the potential for somnolence and other central nervous effects when starting elinzanetant.[1] If patients experience drowsiness, they should refrain from driving or engaging in hazardous occupations until the effects have resolved.[1] In patients with a history of seizures, there is an increased risk of seizure activity with elinzanetant.[1]

Look-alike / Sound-alike Error Risk Potential: No results available in Micromedex.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Decrease in frequency of vasomotor symptoms (at least 2 hot flashes per day or 14 per week)
2) Decrease in severity of vasomotor symptoms (scale of 0 to 3; at least 50% reduction from baseline)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Co-Primary Study Endpoints:

1) LSM change in frequency and severity of vasomotor symptoms at weeks 4 and 12

Table 3. 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. Pinkerton, et al.[1,2] NCT05042362 OASIS 1 DB, MC, PC, Phase 3 RCT	1. Elinzanetant 120 mg PO QDay for 26 weeks 2. Placebo PO QDay for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.	Demographics: -Mean age: 54.6 y -Race Asian: 1% Black: 19% White: 77% -Ethnicity: Hispanic: 8% -Baseline VMS per 24 hours Elinzanetant: 13.4 Placebo: 14.26 -Baseline VMS severity Elinzanetant: 2.56 Placebo: 2.53 -Baseline sleep disturbance score: 61 -Smoking history Elinzanetant: Never: 75% Former: 13% Current: 12% Placebo: Never: 58% Former: 17% Current: 25%	ITT: 1. 199 2. 197 PP: 1. 170 2. 65 Attrition 1. 29 (15%) 2. 32 (16%)	Primary Endpoints: LSM change in frequency of daily moderate to severe hot flashes from baseline to week 4. 1. -7.60 2. -4.31 Difference: -3.29 95% CI, -4.47 to -2.10 P<0.001 LSM change in frequency of moderate to severe hot flashes from baseline to week 12. 1. -8.66 2. -5.44 Difference: -3.22 95% CI, -4.81 to -1.63 P<0.001 LSM change in severity of moderate to severe hot flashes from baseline to week 4. 1. -0.73 2. -0.40 Difference: -0.33	NA NA NA	TEAEs over 12 weeks 1. n = 102 (51.3%) 2. n = 94 (48.5%) Study Discontinuation due to TEAEs at 12 weeks 1. n = 17 (8.5%) 2. n = 13 (6.7%) Serious TEAEs at 12 weeks 1. n = 4 (2%) 2. n = 2 (1%) Headache 1. n = 14 (7%) 2. n = 5 (2.6%) Fatigue 1. n = 14 (7%) 2. n = 3 (1.5%) Arthralgia 1. n = 10 (5%) 2. n = 10 (5.2%)		**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via computer generated assignments. Baseline demographics were generally balanced between groups in both trials, except in smoking history. Unclear if smoking differences were due to poor randomization. Performance Bias: Low. Placebo was identical in appearance to active comparator. Patients, investigators, and outcome assessors blinded to treatment arm. Detection Bias: High. Patients documented frequency and severity of VMS via electronic hand-held device twice a day (morning and evening). Placebo effect may have biased VMS reporting in placebo-treated group. Attrition Bias: High. Dropout rate at 12 weeks was > 10%. Attrition due to adverse events, loss to follow up, and patient decision. Efficacy analysis completed on ITT population. Missing data imputed as last observation carried forward. Reporting Bias: Low. Trial protocol available online. All pre-specified primary and secondary outcomes reported. Other Bias: High. Study funded by the manufacturer. Several authors reported

		Key Inclusion Criteria: -Postmenopausal females aged 40 to 65 y. -Moderate to severe hot flashes and at least 50 over 7 days during screening. Key Exclusion Criteria: -Significant history of cardiac arrythmias -Uncontrolled or treatment-resistant hypertension -Untreated thyroid disease -Unexplained post-menopausal uterine bleeding -Abnormal liver function tests -Current or history of malignancy within the previous 5 years (except basal and squamous cell skin tumors)		95% CI, -0.44 to -0.23 P<0.001 LSM change in severity of moderate to severe hot flashes from baseline to week 12. 1. -0.92 2. -0.52 Difference: -0.40 95% CI -0.54 to -0.25 P<0.001 Secondary Endpoints: LSM change in sleep disturbance from baseline to week 12 as measured by the PROMIS SD SF 8b total t-score. 1. -10.8 2. -5.0 Difference: -5.6 95% CI -7.2 to -4 P<0.001 LSM change from baseline to week 12 in menopause quality of life as assessed by the MENQOL total score. 1. -1.41 2. -0.9 Difference: -0.4 95% CI -0.6 to -0.2 P<0.0001	NA NA NA	95% CI and p-values NR		conflict of interest due to financial support from the manufacturer. **Applicability**: Patient: Most enrollees were White, while observational studies have shown that Black and Hispanic women have a higher incidence of VMS. Enrolled population reflects Oregon Medicaid, but more diverse enrollment would provide broader applicability for this drug. Intervention: Four different doses of elinzanetant (40 mg, 80 mg, 120 mg and 160 mg per day) were evaluated in a Phase 2 RCT. 120 mg once daily was lowest most effective dose. No additional benefit was observed with the 160 mg dose. Comparator: Comparative trials with fezolinetant or hormone replacement therapy or would provide insight into the place of therapy for elinzanetant. Outcomes: Patient-reported reductions in frequency and severity of hot flashes are appropriate but long-term hepatic injury data will be instructive to prescribers. Setting: 77 locations in the United States, Austria, Czechia, Greece, Hungary, Israel, Italy, and the Netherlands.
2. Pinkerton, et al.[1,2] NCT05099159 OASIS 2 DB, MC, PC, Phase 3 RCT	1. Elinzanetant 120 mg PO QDay for 26 weeks 2. Placebo PO QDay for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.	Demographics: -Mean age: 54.8 y -Race Asian: 0.5% Black: 15% White: 84% Hispanic: 8.5% -Ethnicity Hispanic: 9% -Baseline VMS per 24 hours	ITT: 1. 200 2. 200 PP 1. 170 2. 179 Attrition 1. 30 (15%)	Primary Endpoints: LSM change in frequency of moderate to severe hot flashes from baseline to week 4. 1. -8.58 2. -5.54 Difference: -3.04 95% CI -4.40 to -1.68 P<0.001	NA	TEAEs over 12 weeks 1. n = 89 (44.3%) 2.n = 76 (38.2%) Study Discontinuation due to TEAEs at 12 weeks 1. n = 13 (6.5%) 2. n = 4 (2.0%)		**Risk of Bias (low/high/unclear)**: Selection Bias: see OASIS 1 Performance Bias: see OASIS 1 Detection Bias: see OASIS 1 Attrition Bias: see OASIS 1 Reporting Bias: see OASIS 1 Other Bias: see OASIS 1 **Applicability**: Patient: see OASIS 1 Intervention: see OASIS 1

		Elinzanetant: 14.66 Placebo: 16.16 -Baseline VMS severity Elinzanetant: 2.53 Placebo: 2.54 -Baseline sleep disturbance score: 61 Smoking history Elinzanetant: Never: 57% Former: 21% Current: 21% Placebo: Never: 68% Former: 17% Current: 16% <u>Key Inclusion Criteria</u>: see OASIS 1 <u>Key Exclusion Criteria</u>: see OASIS 1	2. 21 (11%)	LSM change in frequency of moderate to severe hot flashes from baseline to week 12. 1. -9.72 2. -6.48 Difference: -3.24 95% CI -4.60 to -1.88 P<0.001 LSM change in severity of moderate to severe hot flashes from baseline to week 4. 1. -0.75 2. -0.53 Difference: -0.22 95% CI -0.34 to -0.09 P=0.0003 LSM change in severity of moderate to severe hot flashes from baseline to week 12. 1. -0.91 2. -0.62 Difference: -0.29 95% CI -0.44 to -0.14 P<0.001 <u>Secondary Endpoints</u>: LSM change from baseline to week 12 in sleep disturbance as measured by the PROMIS SD SF 8b total t score. 1. -10.6 2. -5.5 Difference: -4.3 95% CI -5.8 to -2.9 P<0.001 LSM change from baseline to week 12 in menopause quality of life as assessed by the MENQOL total score. 1. -1.34	NA NA NA NA	<u>Serious TEAEs at 12 weeks</u> 1. n = 1 (0.5%) 2. n = 1 (0.5%) <u>Headache</u> 1. n = 14 (9%) 2. n = 5 (2.5%) <u>Fatigue</u> 1. n = 11 (5.5%) 2. n= 3 (1.5%) <u>Arthralgia</u> 1. n = 5 (2.5%) 2. n= 2 (1%) 95% CI and p-values NR		<u>Comparator</u>: see OASIS 1 <u>Outcomes</u>: see OASIS 1 <u>Setting</u>: 77 sites in the United States, Canada, Czechia, Germany, Italy, Norway, Poland, Portugal, Slovakia, and Switzerland

				2. -0.97 Difference: -0.3 95% CI -0.5 to -0.1 P=0.0059	NA			

Abbreviations: ARR = absolute risk reduction; DB = double-blind; CI = confidence interval; ITT = intention to treat; LSM = least square mean; MC = multi-center; MENQOL = Menopause-Specific Quality of Life; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PO = by mouth; PP = per protocol; PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form; QDay = once daily; RCT = randomized controlled trial; TEAEs = Treatment-emergent adverse events; VMS = vasomotor symptoms; y = years.

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Appendix 1: Prescribing Information Highlights

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

LYNKUET® (elinzanetant) capsules, for oral use
Initial U.S. Approval: 2025

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

LYNKUET is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause. (1)

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

The recommended dosage is 120 mg (two 60 mg capsules) orally once daily at bedtime with or without food. (2.2)

Swallow capsules whole. Do not cut, crush, or chew capsules. (2.2)

See full prescribing information for LYNKUET dosage modification due to drug interactions. (2.3)

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

Capsules: 60 mg (**3**)

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

- Pregnancy. (4)

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

- CNS Depressant Effect and Daytime Impairment: Advise patients about the potential for somnolence and other nervous system effects. Advise patients who experience these effects to refrain from driving or engaging in hazardous occupations or activities until the effects have resolved (5.1)
- Hepatic Transaminase Elevations: Perform bloodwork prior to initiation of LYNKUET to evaluate for hepatic function and injury. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the upper limit of normal (ULN). Perform follow-up evaluations of hepatic transaminase concentration 3 months after initiation. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the ULN or if the total bilirubin is equal to or exceeds two times the ULN. Advise patients to discontinue LYNKUET immediately in case of signs or symptoms suggesting liver injury. (5.2)
- Risk of pregnancy loss: May cause pregnancy loss or stillbirth when administered during pregnancy. Exclude pregnancy in females of reproductive potential prior to initiating LYNKUET. Discontinue if pregnancy is confirmed (5.3)
- Risk of seizures in patients with a history of seizures (5.4)

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

The most frequently reported (≥5%) adverse reactions were headache, fatigue, dizziness and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Strong CYP3A4 Inhibitors and grapefruit (juice): Avoid concomitant use with LYNKUET. (7.1)
- Moderate CYP3A4 Inhibitors: Reduce LYNKUET dosage to 60 mg once daily. (2.2, 7.1)
- Strong and Moderate CYP3A4 Inducers: Avoid concomitant use with LYNKUET. (7.1)

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

- End Stage Renal Disease with or without hemodialysis: Not recommended. (8.6)
- Moderate to Severe Hepatic Impairment: Not recommended. (8.7)

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

Revised: 10/2025

Appendix 2. Elinzanetant Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Neurokinin 1 and Neurokinin 3 receptor antagonist. Neurokinins are part of the neuronal activity which modulates thermoregulation associated with hot flashes.
Oral Bioavailability	52% following oral administration
Distribution and Protein Binding	Volume of distribution after intravenous administration: 137 liters. Plasma protein binding: 99.7%
Elimination	90% of dose is recovered in feces (50% unchanged) and less than 1% is recovered in urine.
Half-Life	45 hours
Metabolism	Metabolized by CYP3A4 hepatic enzymes to yield 3 active metabolites.

Appendix 3: Proposed Prior Authorization Criteria

~~Fezolinetant (Veozah)~~Neurokinin Receptor Antagonists

Goal(s):
To ensure appropriate and safe use of neurokinin receptor antagonists in specified patient populations.

Length of Authorization:
- 6 to 12 months

Requires PA:
- Fezolinetant and elinzanetant

Step Therapy Required Prior to Coverage:
- Prevention of vasomotor symptoms: conventional hormone therapy (see preferred drug list options at (www.orpdl.org)
- 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.

Approval Criteria		
2. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request to treat moderate to severe vasomotor symptoms due to menopause?	**Yes**: Go to #4 Document baseline frequency and severity of vasomotor symptoms_____	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have inadequate effect, intolerance or contraindication to a 30-day trial of menopausal hormone therapy (e.g., estrogen/progestin)? *Contraindications to estrogen include history of breast cancer, hepatic disease, cardiovascular disease, or a venous thromboembolism event. Intolerance to progestin include breast tenderness and vaginal bleeding.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness Refer provider to preferred drug list option for conventional hormone therapy at www.orpdl.org
5. If patient has an intolerance or contraindication to hormonal therapy, do they have an inadequate effect, intolerance or contraindication to a 30-day trial of paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, or gabapentin?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for fezolinetant?	**Yes:** Go to # 7	**No:** Go to #10
7. Is the patient currently taking a CYP1A2 inhibitor (i.e., cimetidine, amiodarone, mexiletine, ciprofloxacin, or fluvoxamine)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: CYP1A2 inhibitors are contraindicated with fezolinetant therapy.	**No:** Go to #8

Approval Criteria		
8. Have baseline renal function tests been obtained?	**Yes:** Go to #9 and document baseline labs_____	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the estimated glomerular filtration rate less than 30 mL/min?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14
10. Is the request for elinzanetant?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient taking a strong CYP3A4 inhibitor, strong CYP3A4 inducer, or moderate CYP3A4 inducer?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the patient taking a moderate CYP3A4 Inhibitor?	**Yes:** Go to #13	**No:** Go to #14
13. Has the dose of elinzanetant been reduced to 60 mg once a day?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Have baseline liver function tests (AST, ALT, Alk Phos, and total bilirubin) been obtained?	**Yes:** Go to #15 Document baseline labs_____	**No:** Pass to RPh. Deny; medical appropriateness.
15. Do liver function tests indicate presence of hepatic injury (i.e., serum transaminase concentrations or total bilirubin greater than 2-times the upper limit of normal)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for 3 months

Renewal Criteria		
1. Have frequency and severity of vasomotor symptoms been reduced from baseline with treatment?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Have LFTs been requested at months 1-, 2-, and 3 after starting treatment with fezolinetant or 3 months after starting elinzanetant?	**Yes:** Go to #3 and document LFT results_____	**No:** Pass to RPh. Deny; medical appropriateness.
3. Do LFTs indicate hepatic injury ~~severe cirrhosis~~ (i.e., serum transaminase concentrations or total bilirubin greater than 2-times the upper limit of normal)?	**Yes**: Pass to RPh. Deny; medical appropriateness.	**No:** Approve for 12 months**.**

P&T/DUR Review: 4/26 (DM); 2/25 (DM) 6/24 (DM)
Implementation: TBD; 3/10/25; 7/1/24

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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OHSU Drug Effectiveness Review Project Summary Report – Pharmaceutical Treatments for Hereditary Angioedema: Prevention and Acute Treatment of Attacks

Date of Review: April 2026

Date of Last Review: June 2021
Literature Search: Through 7/15/2025

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

Plain Language Summary:

- Hereditary angioedema (HAE) is a disorder that can cause swelling in different places in the body. When swelling happens in the face and airway it can be life-threatening. This disorder is passed along by genes and often runs in families. This swelling, also called an attack, can last for several days and can be brought on by trauma, infection, stress, or some medicines in people who have the disorder.
- Medicines for hereditary angioedema either focus on making the swelling go away faster or preventing the swelling from happening at all. Medicines for this class can be given in a vein, an injection into the fat below the skin, or as an oral pill.
- The purpose of this review is to look at new published data comparing medicines for hereditary angioedema.
- There are no studies that compare one medicine to another. All medicines for hereditary angioedema have been studied compared to placebo (sugar pill).[1]
- The United States (US) Food and Drug Administration (FDA) approved three new medicines for hereditary angioedema in 2025. Donidalorsen (DAWNZERA) is for prevention of attacks in people who are at least 12 years old. It is an injection given into the fat below the skin every 4 weeks.[2] Garadacimab-GXII (ANDEMBRY) is used to prevent attacks in people 12 years and older and is given as a monthly injection into the fat below the skin.[3] Sebetralstat (EKTERLY) is given during attacks in people 12 years and older as an oral tablet.[4]
- Providers must send the Oregon Health Authority (OHA) information to document why they are prescribing medications before the Oregon Health Plan (OHP) will pay for the medicine. This process is called prior authorization (PA).

Research Questions:

1. What is the effectiveness of HAE medications for prevention and treatment of attacks?
2. What are the potential harms of HAE medications for prevention and treatment of attacks?
3. Do the listed interventions vary in their effectiveness or potential harms based on patient or disease characteristics (e.g., age, type of HAE)?
4. What are the clinical practice recommendations for medications for prevention and treatment of attacks?

Conclusions:

- There is no direct comparative evidence available to determine efficacy and safety between agents.[1]
- There are 3 new agents which have been approved since last review of this class by the Pharmacy and Therapeutics committee in 2021.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Donidalorsen (DAWNZERA): indicated for prophylaxis of HAE attacks in patients 12 years and older as a subcutaneous (SC) injection every 4 weeks with consideration of every 8 weeks injection interval.[2] There is high certainty evidence that donidalorsen reduced the rate of attacks from approximately 2.25/month to 0.23-0.44/month and moderate certainty evidence of clinical response in 65%-82% of participants ($p<0.05$) when compared to placebo.[1]
- Garadacimab-GXII (ANDEMBRY): indicated for prophylaxis of HAE attacks in patients 12 years and older as a monthly SC injection.[3] Compared to placebo, the monthly attack rate was reduced by 87% over 6 months ($p<0.01$) in the phase 3 trial with a 92-100% response rate from baseline based on moderate certainty evidence.[1] For attacks requiring an on-demand treatment there was a mean of 0.23 attacks on garadacimab compared to 1.86 attacks with placebo based on moderate certainty evidence .[1]
- Sebetralstat (EKTERLY): indicated for acute HAE attacks in patients 12 years and older as an oral tablet.[4] There is low certainty evidence that compared to placebo, sebetralstat had quicker initial and sustained improvements in symptoms, including complete resolution of symptoms and less use of on demand rescue medications. [1]

- Two expanded indications have been granted since the previous class update:
  - Lanadelumab-flyo (TAKZYRO) use was approved in 2023 for patients aged 2 to less than 12 years for prevention of HAE attacks.
  - Berotralstat (ORLADEYO) use was approved in 2025 for patients aged 2 to less than 12 years for prevention of HAE attacks, and an oral pellet formulation is now available.
- The most recent guidelines were published in 2022 by World Allergy Association and European Academy of Allergy and Clinical Immunology (WAA/EAACI).[1] Guidelines were of fair quality.[1] Products recently approved by the Food and Drug Administration after guideline publication were not included in current recommendations. First-line recommendations include:[1]
  - Acute Treatment: Intravenous C1 esterase inhibitors, ecallantide, and icatibant.
  - Acute Treatment in children: C1 esterase inhibitors and icatibant
  - Prophylactic treatment: Plasma-derived C1-esterase inhibitors (intravenous or subcutaneous), lanadelumab, and berotralstat.
  - Prophylactic treatment in children: C1-esterase inhibitors
  - Acute and prophylactic treatment in pregnant people and those breastfeeding: C1-esterase inhibitors
- New randomized controlled trials (RCT) published since last review to support approval of new agents and one new RCT of lanadelumab are summarized in the DERP review. All comparisons were versus placebo and results support current policy for HAE management.

Recommendations:

- Update prior authorization criteria for inclusion of new agents.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

- Therapy for HAE can be divided into 2 types: acute and prophylactic treatment. There is no direct comparative evidence evaluating drugs for either prophylactic or acute treatment of HAE.
- Medications for HAE were last reviewed in June 2021 with a class update and new drug evaluation of berotralstat. The prior authorization criteria were updated to include berotralstat. No other changes were made based on clinical information or evaluation of medication costs in executive session.
- Prior authorization is required for all HAE medications, and certain C1 esterase inhibitors (BERINERT for acute attacks, HAEGARDA for prophylaxis) are preferred. Prior authorization does not apply to treatments administered during emergency department visits or hospitalization.

Methods:
The December 2025 systematic review on "Pharmaceutical Treatments for Hereditary Angioedema: Prevention and Acute Treatment of Attacks" by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. An additional literature search was conducted by Drug Use Research and Management (DURM) in OVID Medline through 2/28/26 to look for comparative evidence from end of DERP literature search date until the present. No direct comparative evidence was identified in that additional search.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Evidence is listed with certainty grading, where high certainty of evidence (CoE) equates to a high degree of confidence in the stated outcome (e.g., difference, or difference) between study groups. OHSU does not recommend or endorse any guidelines or recommendations developed by users of these reports.

Summary Findings:
There were 22 RCTs that met inclusion criteria reporting data in 51 publications with 9 reporting on interventions for acute attacks and 13 RCTs reporting on therapeutics for prevention.[1] Many of these studies were available during previous HAE class update. Additionally, one 2022 guideline of fair quality on the management of prevention of HAE attacks by WAA/EAACI was included.[1] **Appendix 2** includes names and routes of currently approved and marketed products for HAE.

<u>Guideline</u>
World Allergy Association and European Academy of Allergy and Clinical Immunology (WAA/EAACI) Guideline for the Management of Hereditary Angioedema (2021, published 2022)

This revision of the original 2017 guideline was graded as methodologically fair by DERP.[1] The formal GRADE assessments were not reported and the formal systematic review was not provided or cited and external peer review was not mentioned by the guideline committee.[1] Given the 2022 publication data, newer agents for HAE were not included in the recommendations.

The first-line medications for acute attacks are intravenous C1 esterase inhibitors (either plasma-derived or recombinant), icatibant, and ecallantide.[1] Notably, ecallantide must be administered in a health care setting due to risk of anaphylaxis and hypersensitivity reaction.[1]

Short-term prophylaxis prior to procedures (e.g., medical, surgical, or dental) is recommended to include intravenous (IV), plasma-derived, C1 esterase inhibitors administered as close as possible to the procedure.[1] Alternatively, a recombinant C1 esterase inhibitor may be used.[1]

First-line recommendations for long-term prophylaxis are plasma-derived C1 esterase inhibitors (IV or SC), lanadelumab, and berotralstat.[1] The plasma-derived C1 esterase inhibitors are considered equally effective.[1] Lanadelumab may be given SC every 2 weeks, with the option to extend to every 4-week dosing, while berotralstat is an oral product.

For acute attacks in children, C1 esterase inhibitors and icatibant are preferred. Recommended prophylaxis regimens include plasma-derived C1 esterase inhibitors for those under 12 years of age.[1] Ecallantide, lanadelumab, and berotralstat are not recommended for children due to insufficient safety data.[1] Of note, use of icatibant in people under 18 years is off-label in the United States (US), and berotralstat has been approved for use in those 2 years of age and older since publication of these guidelines. Additionally, for pregnant people and those breastfeeding, C1 esterase inhibitors are the preferred and safest therapy for acute attacks and prophylaxis.[1]

Randomized controlled trials

Most of the 22 RCTs included in the DERP report were published prior to previous DURM class updates and do not provide new information to inform policy. There were no direct comparative studies of agents in this class.[1]

Sebetralstat (EKTERLY) was approved by the FDA in 2025 for acute attacks in patients 12 years and older as an oral tablet.[4] Two RCTs, one with low risk of bias (RoB) (n=136, 3-way cross-over with 300 mg sebetralstat, 600 mg sebetralstat, and placebo), the other with moderate RoB (n=68, phase 2, cross-over design) found that versus placebo, sebetralstat had quicker initial and sustained improvements in symptoms, including complete resolution of symptoms (low certainty of evidence [CoE]) and less use of on demand rescue medications (low CoE).[1] In the phase 3 study, there was a significantly shorter median time to symptom relief in participants receiving 300 mg and 600 mg of sebetralstat (1.61 hours; interquartile range [IQR], 0.78 to 7.04 for 300 mg; and 1.79 hours; IQR, 1.02 to 3.79 for 600 mg) than placebo (6.72 hours; IQR, 1.34 to > 12; $P < 0.001$ for 300 mg and $P = 0.001$ for 600 mg, respectively).[1] It was unclear if sebetralstat was associated with a higher risk of adverse events (AE) with short term use (high CoE).[1] At least one AE was experienced by 37% of patients.[1] The most common AEs were headache, nausea, dyspepsia, fatigue, irregular menstruation, rash, dysgeusia, and abdominal pain.[1]

Two new trials were published on the efficacy of lanadelumab, approved for prevention of HAE attacks since the last class update. One was an observational study (n=20). The other was the CASPIAN Study, a 26-week RCT (n=77) that evaluated 300 mg SC every 2 weeks or placebo in patients 12 years or older with at least one HAE attack in the previous 4 weeks while on high-dose antihistamines and history of non-histaminergic angioedema and normal C1 inhibitor function.[1] Investigators-confirmed attacks were recorded during the study period. The model-based mean attack rate of 1.82 attacks/month for lanadelumab and 1.78 attacks/month for placebo did not show statistical significance between groups (rate ratio 1.02; $P= 0.90$). The 2 previously published RCTs did show a significant difference in this comparison. With 2 of 3 published RCTs showing statistical significance in attack rate reductions, there is low CoE in a reduction in rate of HAE attacks with lanadelumab.[1] There is an average of approximately 0.25 attacks/month pooled across the 3 studies.[1] Most participants receiving lanadelumab reported AEs (92%), with injection site pain (30%), arthralgia (14%), and headache (12%) being the most common.[1]

Donidalorsen (DAWNZERA) was approved by the FDA in 2025 for prophylaxis of attacks in patients 12 years and older as a SC injection every 4 weeks.[2] Dosing every 8 weeks may be considered for people who have stable symptoms without attacks.[2] Two RCTs, both rated as low RoB were included; a phase 2 trial (n=20) in adults and a phase 3 trial (N=91) in people age 12 years and older.[1] Compared to placebo, donidalorsen reduced the rate of attacks from approximately 2.25/month to 0.23-0.44/month (high CoE) and demonstrated clinical response in 65%-82% of participants ($p<0.05$) (moderate CoE).[1] Additionally, there was an improvement in the Angioedema Quality of Life (Ae-QoL) score by 18.6 to 20.7 points (minimum clinically important difference is 6 points) (moderate CoE).[1] Adverse events were generally mild (high CoE) with no severe AEs.[1]

Garadacimab-gxii (ANDEMBRY) was approved by the FDA in 2025 for prophylaxis of attacks in patients 12 years and older as a SC injection monthly.[3] Two RCTs, both rated as having low RoB were included.[1] A phase 2 trial (n=32) with a duration of 12 weeks included 3 garadacimab doses (75 mg, 200 mg, or 600 mg).[1]

The 600 mg dose was not found to provide additional clinical benefit.[1] A phase 3 RCT (n=65) was conducted using a 400 mg loading dose followed by 200 mg monthly dosing for 6 months in patients with type I or type II HAE.[1] Compared to placebo, the monthly attack rate was reduced by 87% ($p<0.01$) in the phase 3 RCT and 100% ($p<0.01$) in the phase 2 RCT (moderate CoE) with a 92-100% response rate from baseline (moderate CoE).[1] For attacks requiring an on-demand treatment there was a mean of 0.23 attacks on garadacimab compared to 1.86 attacks with placebo (moderate CoE).[1] The AEs were generally mild, and no severe AEs were reported (moderate CoE).[1]

Reference:

1. Lindsey W, Hartsell F, Bricken L, Trinidad K, Key C, Krehling K, Hepburn Z, Davis L, Grabowsky A. Pharmaceutical treatments for hereditary angioedema: prevention and acute treatment of attacks. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2025.
2. Dawnzera (donidalorsen) package insert. Carlsbad, CA. Ionis Pharmaceuticals. August 2025.
3. Andembry (garadacimab-gxii) package insert. King of Prussia, PA. CSL Behring LLC. June 2026.
4. Ekterly (sebetralstat). package insert. Cambridge, MA. KalVista Pharmaceuticals Inc. July 2025.

Appendix 1: Current Preferred Drug List*

Generic	Brand	Route	Form	PDL
C1 esterase inhibitor	BERINERT	INTRAVEN	KIT	Y
C1 esterase inhibitor	BERINERT	INTRAVEN	VIAL	Y
C1 esterase inhibitor	HAEGARDA	SUBCUT	VIAL	Y
C1 esterase inhibitor	CINRYZE	INTRAVEN	VIAL	N
C1 esterase inhibitor, recomb	RUCONEST	INTRAVEN	VIAL	N
berotralstat hydrochloride	ORLADEYO	ORAL	CAPSULE	N
sebetralstat	EKTERLY	ORAL	TABLET	N
donidalorsen sodium	DAWNZERA	SUBCUT	AUTO INJCT	N
icatibant acetate	FIRAZYR	SUBCUT	SYRINGE	N
icatibant acetate	ICATIBANT	SUBCUT	SYRINGE	N
icatibant acetate	SAJAZIR	SUBCUT	SYRINGE	N
lanadelumab-flyo	TAKHZYRO	SUBCUT	SYRINGE	N
ecallantide	KALBITOR	SUBCUT	VIAL	N
lanadelumab-flyo	TAKHZYRO	SUBCUT	VIAL	N

*Garadacimab-gxii (ANDEMBRY) subcutaneous injection not listed in First Data Bank as of 3/3/26.

Hereditary Angioedema

Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and provider administered claims).

  NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

Covered Alternatives:

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

Table 1. FDA Approved indications and dosing for hereditary angioedema treatments

Drug Name	Place in Therapy	FDA Indication(s)	Dose and Frequency
C1 esterase inhibitor (Berinert®)	Acute	Abdominal, facial, or laryngeal attacks	20 units/kg intravenously as a single dose
C1 esterase inhibitor, recombinant (Ruconest®)	Acute	Attacks in adults and adolescents. Efficacy has not been established in laryngeal attacks.	50 units/kg intravenously as a single dose; maximum dose: 4,200 units; may repeat once within 24 hours if attack continues
Ecallantide (Kalbitor®)	Acute	Attacks in patients ≥12 years of age	30 mg as a one-time dose (3 subcutaneous injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Acute	Attacks in adults ≥18 years of age	30 mg injection once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
Sebetralstat (Ekterly®)	Acute	Attacks in patients ≥12 years of age	600mg (2 tablets) orally; may repeat a second 600 mg dose after 3 hours if response inadequate; maximum dose per 24 hours: 1200 mg
Berotralstat (Orladayo™)	Prophylaxis	HAE prophylaxis in patients ≥212 years of age	110 mg or 150 mg orally daily (capsules) 72, mg 96 mg, 108 mg, or 132 mg orally daily (weight based; pellets)

C1 esterase inhibitor (Cinryze®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	1,000 units intravenously every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor (Haegarda®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	60 units/kg subcutaneous every 3 to 4 days (twice weekly)
Donidalorsen (Dawnzera™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	80 mg subcutaneous injection every 4 weeks; may consider 8-week interval
Garadacimab-gxii (Andembry®)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	400 mg loading dose (two subcutaneous injections); then 200 mg subcutaneously monthly
Lanadelumab-flyo (Takhzyro™)	Prophylaxis	HAE prophylaxis in patients ≥2 years of age	300 mg subcutaneous injection every 2 weeks (for ≥12 years) or 150 mg every 2 weeks (for 6-12 years); may consider dosing every 4 weeks for patients who are well-controlled for > 6 months; 150 mg every 4 weeks for 2-6 years of age

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for an FDA approved indication and place in therapy according to **Table 1** and is there confirmed laboratory diagnosis of hereditary angioedema (e.g., low C4 levels and either low C1 inhibitor antigenic levels or low C1 inhibitor functional levels)?	**Yes**: Go to #4 Document labs	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Notify provider of potential serious adverse effects of therapy. See notes below.
5. Is the request for a C1 esterase inhibitor or ecallantide?	**Yes:** Go to #6	**No:** Go to #7
6. Is the patient prescribed concurrent epinephrine, or do they have epinephrine on hand?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the medication intended to be administered by a non-healthcare professional (e.g., self-administered)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the member received training on identification of an acute attack?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the request for treatment of an acute hereditary angioedema attack?	**Yes:** Go to #12 Document attack severity if available	**No:** Go to #10
10. Is the request for prophylactic use in a patient with a history of hereditary angioedema attacks?	**Yes:** Go to #11 Document baseline number of attacks in the last 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
11. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. 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 & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for the following recommended durations: Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**) Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	**Yes:** Go to #2	**No:** Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Go to #3

Renewal Criteria		
3. Does the patient currently already have at least one on-demand dose for an acute attack?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Pass to RPh. Deny; medical appropriateness.
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	**Yes:** Go to #6 Document change in attack frequency or severity	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	**Yes:** Go to #7	**No:** Approve for up to 12 months.
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

<u>Notes on adverse effects of treatment:</u>

Berotralstat

- Doses above 150 mg daily have been associated with QT prolongation. Dose adjustment is recommended for patients with moderate to severe hepatic impairment or with concomitant p-glycoprotein or BCRP inhibitors. Avoid use with p-glycoprotein inducers.

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.

- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide
- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.
- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant
- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

Lanadelumab-flyo
- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.

P&T/DUR Review: 6/21 (SS); 3/19 (SS)
Implementation: 7/1/2021; 5/1/19

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Drug Class Update Focused for Pelvic pain and Dysmenorrhea: GnRH Agonists and Antagonists

Date of Review: April 2026

Date of Last Review: 12/2021 (GnRH agonists); 2/2023 (GnRH antagonists)
Dates of Literature Search: 06/20/2023 – 01/06/2026

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

Purpose for Class Update:
Review medications approved to manage pelvic pain and dysmenorrhea to confirm Oregon Health Plan (OHP) Fee for Service (FFS) polices align with Health Evidence Review Commission (HERC) Guidance for these conditions. With the implementation of the Benefit Plan Update (BUP) in January 2027, a pathway to coverage for medications to treat previously unfunded conditions will be necessary.

Plain Language Summary:
- Painful menstrual cramps, also known as dysmenorrhea, are experienced by many women during their reproductive years. Symptoms can include cramps, nausea, vomiting, diarrhea, dizziness, and headaches. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen are the first treatments usually given for managing pain caused by dysmenorrhea. If these medicines do not relieve the pain, a hormonal birth control medicine may be prescribed. For some women, a hormonal intrauterine device (IUD) can be used to treat painful periods.
- Some types of dysmenorrhea can be caused by endometriosis or uterine fibroids and can also cause infertility, or difficulty getting pregnant.
- Fibroids are solid growths that form on the outside, or the inside, or in the walls of the uterus. Fibroids are usually noncancerous (benign), but they can cause heavy menstrual bleeding, pelvic pressure, frequent urination, and lower back pain.
- Endometriosis occurs when endometrium (the tissue lining the inside of the uterus) starts growing in other parts of the body such as on the ovaries, fallopian tubes, or bladder. Later in the menstrual cycle, this tissue may break down and shed the in the body. This can cause pain throughout the entire month. The most common symptoms of endometriosis include painful periods, pelvic pain between periods, and pain with sexual intercourse.
- The most common treatments to relieve pain associated with endometriosis and fibroids are hormone therapies, like birth control pills and gonadotropin-releasing hormone (GnRH) analogs. Hormone therapies are medicines that decrease the amount of estrogen in the body. Less estrogen will slow the growth of endometrial tissue and stop more lesions from forming outside the uterus. Less estrogen can also shrink fibroids, which makes it easier to remove them surgically.
- Certain kinds of birth control pills (such as estradiol combined with norethindrone), and medicines called GnRH analogs (leuprolide, elagolix, relugolix), stop the production of hormones that tell the ovaries to make estrogen, which decreases the amount of endometrial tissue that grows every month. Many women have lighter and shorter menstrual flows (periods) when they take birth control pills. Some GnRH analogs may create an artificial menopause, and

monthly periods are prevented. The risk of bone loss when taking these medicines is very high, which prevents people from taking these medicines for longer than 24 months.

- OHP FFS pays for birth control pills when prescribed for adolescents and adults and they do not require prior authorization. Providers must explain to the Oregon Health Authority (OHA) why a patient needs a GnRH analog before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the comparative evidence assessing efficacy GnRH agonists and antagonists to other drug therapies for the treatment of moderate to severe pain associated with pelvic pain and dysmenorrhea?
2. What is the comparative evidence assessing safety of GnRH agonists and antagonists to other drug therapies for the treatment of moderate to severe pain associated pelvic pain and dysmenorrhea?
3. Are there any subgroups (based on age, race, ethnicity, comorbidities, disease duration, or severity) that would particularly benefit or be harmed from treatment with GnRH agonists or antagonists for pelvic pain or dysmenorrhea associated with endometriosis or uterine fibroids?

Conclusions:

- Since the last review, 3 systematic reviews[1-3] and 4 guidelines[4-8] have been published or updated to assess therapies used for management of primary dysmenorrhea, uterine fibroids, or endometriosis.
- In May 2025 the Society of Obstetrics and Gynecology Canada (SOGC) issued guidance for management of primary dysmenorrhea.[4]
    - Health care providers should offer NSAIDs or acetaminophen, administered with regular dosing regimens, as a first-line treatment for most women with primary dysmenorrhea unless contraindicated (strong recommendation, high-quality evidence).[4]
    - Continuous or extended use combined hormonal contraceptives are recommended for the treatment of dysmenorrhea (strong recommendation, high-quality evidence).[4]
- A 2025 Cochrane Review assessed the benefits and risks of medical treatments prior to surgery for uterine fibroids.[1] Pretreatment with GnRH analogs (i.e. leuprolide, goserelin, and triptorelin) may reduce uterine and fibroid volume compared to placebo and other medical therapies and probably increases preoperative hemoglobin levels, but probably also increases the number of adverse events (low certainty evidence).[1] Blood transfusions and operation time during hysterectomy may be reduced with GnRH analogs compared to placebo with fewer women experiencing postoperative morbidity (low certainty evidence).[1]
- Canada's Drug Agency (CDA) Canadian Drug Expert Committee (CDEC) recommends that the GnRH antagonist, relugolix-estradiol–norethindrone acetate, be reimbursed for the management of heavy menstrual bleeding associated with uterine fibroids in patients (2025).[5]
- The National Institute for Health and Care Excellence (NICE) recommends relugolix–estradiol–norethindrone as an option for treating moderate to severe symptoms of uterine fibroids (2022) or endometriosis in adults of reproductive age (2024).[6,7]
- A 2023 Cochrane Review assessed the effectiveness of GnRH agonists (goserelin, leuprolide, nafarelin, and triptorelin) in the treatment of painful symptoms associated with endometriosis.[2] For relief of overall pain, there may be a slight decrease in favor of treatment with GnRH agonists compared to placebo or oral or injectable progestogens (low certainty evidence).[2] The effects on alleviating pain are uncertain when comparing GnRH agonists with danazol or intra-uterine progestogens.[2] There may be a slight increase in adverse effects when women are treated with GnRH agonists, compared to placebo (very low certainty evidence).[2]
- A 2025 Cochrane Review evaluated the harms and benefits of progestogens in the treatment of endometriosis-associated pain symptoms.[3] In individuals with endometriosis, oral progestogens compared with placebo likely reduce overall pain and dysmenorrhea and may reduce pelvic pain (moderate certainty

evidence) .[3] Compared with other hormonal suppression strategies (i.e., oral contraceptives, GnRH agonists), the evidence is less certain due to the small number of studies for each comparison and outcome.[3]

- The European Society of Human Reproduction and Embryology (ESHRE) guidance for management of endometriosis was updated in February 2022.[8] Treatment should begin with NSAIDs/analgesics and/or hormonal treatments (combined oral contraceptives, progestogens).[8] Second-line treatments include a GnRH agonist (i.e., leuprolide) or GnRH antagonists (i.e., elagolix, relugolix).[8] Strength of recommendations and quality of evidence are as follows:
    - Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain (weak recommendation; very low-quality evidence).[8]
    - It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain (strong recommendation; low-quality evidence).[8]
    - It is recommended to prescribe GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (strong recommendation; low-quality evidence).[8]
    - Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypo-estrogenic symptoms (strong recommendation; moderate-quality evidence).[8]
    - It can be considered to prescribe GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (weak recommendation; moderate-quality evidence).[8]
- New Food and Drug Administration (FDA) safety alerts for GnRH agonists are presented in **Table 3**.
- There is insufficient evidence that any subgroups (based on age, race, ethnicity, comorbidities, disease duration, or severity) that would particularly benefit or be harmed from treatment with GnRH agonists or GnRH antagonists for pelvic pain or dysmenorrhea associated with endometriosis or uterine fibroids.

Recommendations:

- No changes to the PDL are recommended based upon recent published guidelines and systematic reviews.
- Modify PA criteria for GnRH agonists and GnRH antagonists to align with HERC guidance.
- Evaluate drug costs in executive session.

Summary of Prior Reviews and Current Policy:

- A drug class update that reviewed drugs for management of endometriosis and uterine fibroids was presented to the Pharmacy and Therapeutics (P & T) committee in December 2021. The committee accepted a recommendation to implement new prior authorization (PA) criteria for GnRH analogs to evaluate GnRH antagonists (e.g., relugolix, elagolix), separately from GnRH agonists (e.g., leuprolide). PA criteria are presented in **Appendix 5**.
- The GnRH antagonists were last reviewed by the P & T committee at the February 2023 meeting. At that time, PA criteria were revised for relugolix, estradiol, and norethindrone combination therapy to include management of moderate to severe pain associated with endometriosis in premenopausal women in addition to management of heavy menstrual bleeding associated with uterine fibroids (**Appendix 5**).
- The pediatric formulation of leuprolide is the only preferred GnRH agonist on the preferred drug list (PDL). All other GnRH agonists and antagonists are non-preferred on the PDL and are presented in **Appendix 2**.

Background:

The HERC has issued guidance for the management and treatment of pelvic pain and dysmenorrhea, which are not currently funded diagnoses.[9] The complete guidance is presented in **Appendix 1.** For management of dysmenorrhea a hysterectomy may be indicated if a 6-month trial of NSAIDs and hormonal therapeutic

options are ineffective or contraindicated. Hormonal options include: a) contraceptives, progesterone-containing IUD, or injectable hormone therapy or b)GnRH analogs or danazol.[9] For diagnostic magnetic resonance imaging (MRI) or surgical management of pelvic pain syndrome, a 6-month trial of NSAIDs and a) oral contraceptives, progesterone-containing IUD, or injectable hormone therapy or b) GnRH agonists or danazol must be proven ineffective or contraindicated.[9]

Dysmenorrhea

Dysmenorrhea, or painful menstruation, is experienced by many female assigned at birth people in their reproductive years.[10] Dysmenorrhea is characterized by severe, painful, cramping in the lower abdomen that is often accompanied by sweating, headaches, nausea, vomiting, muscle cramps, and diarrhea.[11] Primary dysmenorrhea is defined as painful menstruation in the absence of pelvic pathology.[11] Secondary dysmenorrhea is due pelvic pathology such as endometriosis, adenomyosis, pelvic inflammatory disease, congenital anatomic abnormalities, or uterine fibroids.[11] Primary dysmenorrhea is a result of the cyclooxygenase pathway producing increased leukotrienes and prostaglandins.[12,13] The increased prostaglandins cause uterine contractions that restrict blood flow and lead to the production of metabolites that stimulate pain receptors.[12] The diagnosis of primary dysmenorrhea is made more often in adolescents and young women with estimates ranging from 67% to 90% for those aged 17–24 years.[11] In general, increased severity of dysmenorrhea has been suggested to relate to age, smoking, earlier age at menarche, nulliparity, longer and heavier menstrual flow, and family history of dysmenorrhea.[11]

First-line treatment options for primary dysmenorrhea include NSAIDs, acetaminophen, and/or hormonal contraception.[4] Nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen effectively manage dysmenorrhea by decreasing prostaglandin levels via inhibition of cyclooxygenase-mediated production.[14] The NSAID should be started with the onset of symptoms or menses and continued through day 2 or 3 of the menstrual cycle.[13,14] Hormonal contraception includes combined estrogen-progestin products (oral pills, transdermal patches, and vaginal rings) and progestin-only options (implant, injection, IUD, and oral pills). Hormonal agents inhibit proliferation of the endometrial lining, which decreases leukotriene and prostaglandin production.[14] Choice of treatment order depends on the clinical needs and preferences of the patient.[13]

Uterine Fibroids

Uterine fibroids (i.e., leiomyomas) are benign, hormone-dependent, smooth muscle tumors of that arise primarily in 3 regions of the uterus (submucosal, intramural, and subserosal) in women of reproductive age.[15] Although they are often asymptomatic, uterine fibroids can cause excessive menstrual bleeding, pelvic pain, and other symptoms that seriously affect a woman's quality of life.[16] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[17] Other fibroid symptoms include infertility, increased urinary frequency or incontinence, constipation, abdominal bloating, dyspareunia, and fatigue (due to anemia from heavy bleeding).[16] The evaluation of fibroids is based mainly on the patient's presenting symptoms: abnormal menstrual bleeding, bulk symptoms (i.e., abdominal protrusion, constipation or urinary frequency), pelvic pain, or findings suggestive of anemia.[15] Fibroids are sometimes found in asymptomatic women during routine pelvic examination or incidentally during imaging.[15]

In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[16] Uterine fibroids account for nearly 30% of all hysterectomies among American women ages 18–44 years.[16] Factors that are associated with an increased risk of uterine fibroids include premenopausal status, family history, nulliparity, hypertension, and obesity.[18] On average, Black women are younger at onset of fibroids, and have larger and more numerous tumors, and are more likely to be anemic and have surgical interventions for fibroids.[16] These observed differences are likely due to inequities in social determinants of health as well as implicit and explicit bias among the medical community.[19] In addition, differences in social determinants of health such as limitations on access to quality education, jobs, stable housing, safe neighborhoods, nutritious foods, and health insurance are associated with inequitable uterine fibroid treatment among Black women.[20,21] Racial disparities in treatment, such as higher rates of hysterectomy and myomectomy (compared with nonsurgical therapy) and open

hysterectomy (compared with minimally invasive approaches) have been reported among Black women compared with White women.[20] The prevalence of uterine fibroids does not appear to be higher among Hispanic and Asian women as compared with White women, but data are far more limited for these populations.[20]

The alkaline hematin technique, which involves chemically measuring the blood content of used sanitary products, is considered the gold standard for menstrual blood loss determination and has traditionally been used to diagnose heavy menstrual bleeding.[22] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[17] The alkaline hematin method directly measures the volume of menstrual blood loss by comparing hematin from menstrual products against calibration curves created from a simultaneous venous blood sample.[23] The alkaline hematin laboratory testing of blood stained sanitary products has been utilized as a primary endpoint in a number of trials evaluating heavy menstrual bleeding with the levonorgestrel-releasing IUD, oral contraceptives, and leuprolide.[24] The FDA has found this test to be somewhat more objective than a pictorial bleeding assessment which directs the study participant to grade their volume of bleeding by comparing their sanitary products to pictures of sanitary products that have undergone some degree of saturation with known quantities of blood.[24]

Symptomatic fibroids may require medical or surgical intervention.[16] Surgical treatment includes hysterectomy, myomectomy, uterine artery embolization, and magnetic resonance–guided focused ultrasound surgery.[15] The 3 medications that have FDA-approval for managing fibroid-related bleeding are the GnRH agonist, leuprolide acetate[25] and the 2 GnRH antagonists combined with add-back hormonal therapy (i.e., elagolix and relugolix).[26,27] Several medications including oral contraceptives, levonorgestrel-releasing IUD (LNG-IUD), and tranexamic acid are used to manage heavy menstrual bleeding associated with fibroids. The 2021 American College of Obstetricians and Gynecologists (ACOG) practice bulletin recommended treatment options to reduce bleeding due to uterine leiomyomas include GnRH antagonists, LNG-IUD, oral contraceptives, and tranexamic acid.[28] Medications that reduce bleeding and leiomyoma size include the GnRH agonists and selective progesterone receptor modulators (ulipristal, mifepristone).[28] Selective progesterone receptor modulators are not FDA-approved for management of bleeding due to fibroids.[3] A summary of the ACOG recommendations is presented in **Table 1.**

Table 1. Medical Management of Uterine Fibroids[28]

Medication (BRAND NAME)	Availability	Notes
Combined Estrogen-Progestin Contraceptives	Oral, vaginal ring, transdermal patch	Off-label use of hormonal contraceptives
High Dose Oral Progestogens	Oral, implants, injections	Off-label use of oral progestogens
Levonorgestrel (MIRENA)	Intrauterine device	Limited evidence for efficacy in treating fibroid-associated pain, effective in reducing bleeding associated with fibroids.
Tranexamic Acid	Oral	Contraindicated in patients at risk for thrombosis
Progesterone Receptor Modulators (Ulipristal, Mifepristone)	Oral	Not approved by the Food and Drug Administration for fibroid bleeding. Ulipristal use is restricted due to hepatic toxicity.
Elagolix-Estradiol-Norethindrone (ORIHANN)	AM oral dose: Elagolix 300 mg plus estradiol 1 mg and norethindrone 0.5 mg PM oral dose: Elagolix 300 mg	Maximum duration of therapy: 24 months
Relugolix-Estradiol-Norethindrone (MYFEMBREE)	Once daily oral dose: Relugolix 40 mg plus estradiol 1 mg and norethindrone 0.5 mg	Maximum duration of therapy: 24 months

Leuprolide Depot Suspension (LUPRON-DEPOT)	Intramuscular injection	Maximum preoperative duration of therapy: 3 months prior to surgery

Slow-release injectable leuprolide acetate received FDA approval in 1999 for preoperative management of patients with anemia caused by uterine fibroids.[29] Leuprolide for this indication is limited to 3 months of use. The recommended dosing regimens for uterine fibroids are 3.75 mg once a month for 3 months or a single 11.25 mg injection.[29] These regimens were found to increase hematocrit by 6% or more and hemoglobin by 2 g/dL or more in 77% of study participants at 3 months of therapy.[30] Although not listed as part of the indication, some clinicians found that the reduction in size of fibroids from leuprolide acetate treatment resulted in less surgical blood loss and less need for blood transfusions.[30] Leuprolide acetate is also FDA approved for management of endometriosis-associated pain and several non-gynecologic indications.[29,31]

Elagolix and relugolix are GnRH receptor antagonists. Both drugs competitively bind to pituitary GnRH receptors, blocking binding of endogenous GnRH with reversible, dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which then decreases estradiol and progesterone production.[32,33] Elagolix and relugolix are available as oral products and are formulated with low-dose hormonal add-back therapy to limit hypoestrogenic side effects such as hot flushes, increased mean serum lipid levels and bone mineral density (BMD) loss.[28] Elagolix in combination with estradiol and norethindrone acetate (ORIAHNN), received FDA-approval in May 2020 for the treatment of fibroid-related heavy menstrual bleeding in premenopausal women.[26] In May 2021 a comparable preparation, relugolix with estradiol and norethindrone acetate (MYFEMBREE), was approved by the FDA for the for the same indication.[27] Due to the risk of menopausal symptoms and reduction of BMD, both medications should only be taken for a maximum duration of 24 months.

According to 2018 NICE guidance, women with heavy menstrual bleeding associated with fibroids can start combined hormonal contraceptives containing estrogen and a progestogen to reduce menstrual blood loss.[34] This is an off-label use of oral contraceptives. Levonorgestrel-releasing IUDs have been found to decrease heavy menstrual bleeding in patients with and without uterine fibroids.[28] However, rates of IUD expulsion are higher in patients with uterine fibroids compared with patients without fibroids (11% versus 0 to 3%).[28] The risk of expulsion may be particularly increased in patients with uterine fibroids that distort the uterine cavity.[28] There is insufficient evidence to support the use of a levonorgestrel-IUD for the treatment of uterine fibroid symptoms other than bleeding.[35]

Tranexamic acid is an oral nonhormonal antifibrinolytic agent FDA-approved for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential.[36] Women who cannot or do not wish to take hormonal contraceptives may prefer this treatment. Tranexamic acid 1,300 mg three times a day can be taken for up to 5 days during monthly menstruation to reduce bleeding.[36] Due to the risk of thrombosis, tranexamic acid is contraindicated in patients at risk for thromboembolic disease or when used concomitantly with hormonal contraceptives.[36] Efficacy of tranexamic acid in women with fibroid-associated heavy menstrual bleeding has not been established.[28]

<u>Endometriosis</u>

Endometriosis is caused by the growth of endometrial-like tissue which implants outside of the uterus on the ovaries, fallopian tubes, bladder, or bowel.[37] The growth is estrogen dependent, and endometrial tissue proliferates and sheds with the menstrual cycle.[37] The chronic inflammation and scarring results in chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[5] Quality of life and work productivity are negatively impacted by endometriosis pain.[6]

Epidemiologic studies have concluded that women with early menarche (<10 years old), with more frequent menstrual cycles (<28 days), family history of endometriosis, and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[5]

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. The Patient Global Impression of Change (PGIC) is a general tool used to evaluate the overall health status as perceived by the patient using a seven-point single-item scale ranging from 'very much worse' to 'very much improved'. [14] The PCIG has been applied as a valid tool in many clinical trials of analgesics but it lacks ability to reflect degrees of change within specific domains.[14] For pain assessment, the visual analogue or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[15] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[15] A similar pain assessment tool commonly used is the Brief Pain Inventory (BPI) which has the added benefit of assessing both pain severity and interference it has on various aspects of daily activities.[16] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[16] A specific tool known as the Biberoglu and Behrman (B&B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as pelvic tenderness and induration.[16] The B&B is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[16] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[16] Quality of Life (QoL) assessment tools such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the European Quality of Life in 5 Dimensions (EQ-5D) have been developed for use in many medical conditions, but there has not been a strong correlation found between QoL and pain intensity with use of these scales in endometriosis patients.[16] The Endometriosis Health Profile (EHP) is a disease-specific instrument used to assess the quality of life in women with endometriosis.[16] The EHP-5 is a shorter version of the EHP-30.[16] Both explore the same five core dimensions including pain, control and powerlessness, emotional well-being, social support, and self-image.[16] The EHP-30 has been validated for use in women with endometriosis, while the EHP-5 has not. [16]

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[38] Although available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[38] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[39] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis.[39] Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[40] Current first-line therapies to manage pain associated with endometriosis are continuous combined oral contraceptives (COCs) or progeestogens.[41] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[40,42] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[41]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy or in combination with a LNG-IUD.[41] Gonadotropin-releasing hormone agonists (i.e. goserelin, leuprolide, and nafarelin) initially stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in a temporary increase of ovarian steroidogenesis.[39] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[40,42] Goserelin and nafarelin are FDA-approved for up to 6 months of continuous use for treatment of pelvic pain caused by endometriosis while leuprolide is FDA-approved for a maximum duration of 12 months.[40] The 12-month treatment limitation is due to concern about the significant bone loss that occurs with GnRH agonist therapy. Add-back therapy or the simultaneous use of estrogen and progestin, progestin alone, or progestin plus a bisphosphonate may alleviate some of the GnRH agonist side effects including bone loss.[41]

The GnRH antagonist, elagolix is indicated to manage moderate-to-severe pain associated with endometriosis and is FDA-approved as a once-daily low dose (150 mg) or a twice-daily high dose (200 mg).[32] However, due to hypoestrogenic-induced declines in BMD, treatment should be maintained for a maximum duration

of 24 months for the low-dose regimen (6 months in patients with moderate hepatic impairment) and 6 months for a high-dose regimen.[32] Relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone) received FDA approval for management of pain associated with endometriosis in 2022.[33] Use of relugolix combination therapy should be limited to 24 months due to the risk of continued bone loss that may not be reversible.[33] **Table 2** outlines the pharmacotherapies used for management of symptoms associated with endometriosis.

Table 2. Medications for Management of Endometriosis[43]

Drug Name (BRAND NAME)	**Formulation**	**Safety Precautions (Boxed Warning in Bold)**
Combined estrogen/progestogen contraceptives	Oral, vaginal ring, transdermal patch	**- Cigarette smoking increases the risk of serious cardiovascular events, particularly in women over 35 years of age** -Increased risk of gall bladder disease
Danazol (DANOCRINE)	Oral Capsule: 50 mg, 100 mg, 200 mg	**-Thrombotic events including strokes** **-Peliosis hepatis and benign hepatic adenoma** **-Intracranial hypertension** **-Use in pregnancy is contraindicated** -Lipoprotein changes -Androgen effects
Gonadotropin Releasing Hormone Agonists		
Goserelin acetate (ZOLADEX)	Subcutaneous Implant: 3.6 mg	-Hyperglycemia -Loss of BMD -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (LUPRON-DEPOT)	Intramuscular depot Injection: 1-month: 3.75 mg 3-month: 11.25 mg	-Loss of BMD -Use in pregnancy is contraindicated -Maximum duration of therapy for endometriosis is 12 months due to concerns of BMD loss.
Nafarelin acetate (SYNAREL)	Nasal Spray: 200 mcg/actuation	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Progestogens		
Medroxyprogesterone acetate (DEPO-SUBQ PROVERA) (DEPO-PROVERA)	Subcutaneous Depot Injection: 104 mg	-**Loss of BMD** -Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Ectopic pregnancy -Menstrual bleeding irregularities -Use in pregnancy is contraindicated

	Intramuscular injection: 150 mg	
Etonogestrel (NEXPLANON)	Subdermal Implant: 68 mg	-History of thrombosis -Active liver disease -History of breast cancer -Use in pregnancy is contraindicated
Norethindrone Acetate	Oral Tablet: 5mg	-Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine) -Worsening depression -Increased risk for thrombosis -Bleeding irregularities -Ectopic pregnancy -Adverse effects on lipid metabolism -Use in pregnancy is contraindicated
Medroxyprogesterone (PROVERA)	Oral Tablet: 10 mg	-**Cardiovascular disorders and breast cancer** **-**Active liver disease -Use in pregnancy is contraindicated
Levonorgestrel (MIRENA)	Intrauterine device: 52 mcg	-Breast cancer -Uterine cancer -Active liver disease - Use in pregnancy is contraindicated
Gonadotropin-Releasing Hormone Antagonists		
Elagolix (ORILISSA)	Oral Tablet: 150 mg, 200 mg	-Decreased BMD -Suicidal ideation -Hepatic transaminase elevations -Use in pregnancy is contraindicated
Relugolix, Estradiol, and Norethindrone (MYFEMBREE)	Oral Tablet: relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg	-**Thromboembolic disorders and vascular events** -Decreased BMD -Breast cancer or other hormone-sensitive malignancies -Suicidal ideation and mood disorders -Hepatic impairment or transaminase elevations -Gallbladder disease or history of cholestatic jaundice -Hypertension -Menstrual bleeding irregularities -Use in pregnancy is contraindicated
Abbreviations: BMD = bone mineral density		

Methods:

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

Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

Cochrane Review: Preoperative Medical Therapy Before Surgery For Uterine Fibroids

A 2025 Cochrane Review assessed the benefits and risks of medical treatments prior to surgery for uterine fibroids.[1] This was an update of a 2017 review. Literature was searched through August 2024.[1] Forty-one RCTs (n = 3,982) met inclusion criteria.[1] Thirty-six studies evaluated GnRH analogs (leuprolide, goserelin, and triptorelin) the comparators were no pretreatment (19 studies), placebo (9 studies), or other medical pretreatments (progestin, selective-progesterone receptor modulators [SPRMs], selective estrogen receptor modulators [SERMs; raloxifene], dopamine agonists, and estrogen receptor antagonists) (8 studies).[1] Five studies evaluated SPRMs versus placebo.[1] Most results provided low-certainty evidence due to poor reporting of randomization procedures, lack of blinding, imprecision and inconsistency. Some outcomes were not measured or did not have usable data.[1] The use of ulipristal acetate (an SPRM) was suspended in March 2025 because of an association with cases of liver failure.[1]

Compared to placebo or no treatment, GnRH analog pretreatment reduces uterine volume (mean difference [MD] −175.34 mL, 95% confidence interval [CI]−219.04 to −131.65; 13 studies, 858 participants; I^2 = 67%; low-certainty evidence) and fibroid volume (MD range 5.7 mL to 155.4 mL; 5 studies to heterogeneous to pool, 427 participants; low-certainty evidence), and probably increases preoperative hemoglobin (MD 0.88 g/dL, 95% CI 0.68 to 1.08; 10 studies, 834 participants; I^2 = 0%; moderate-certainty evidence).[1] However, there is probably a greater likelihood of adverse events with GnRH analogs (odds ratio (OR) 2.78, 95% CI 1.77 to 4.36; 5 studies, 755 participants; I^2 = 28%; moderate-certainty evidence). No usable data were available for preoperative bleeding.[1]

Duration of hysterectomy surgery may be reduced amongst women who receive GnRH analog treatment compared to placebo or no pretreatment (−9.59 minutes, 95% CI −15.9 to -3.28; 6 studies, 617 participants; I^2 = 57%; low-certainty evidence).[1] There were fewer blood transfusions with GnRH analogs compared to placebo or no pretreatment (OR 0.54, 95% CI 0.29 to 1.01; 6 studies, 601 participants; I^2 = 0%; moderate-certainty evidence) and less postoperative morbidity (OR 0.54, 95% CI 0.32 to 0.91; 7 studies, 772 participants; I^2 = 28%; moderate-certainty evidence).[1]

GnRH analogs may be associated with a greater reduction in uterine volume than other medical therapies (−47% compared to −20% and −22% with use of 5 mg and 10 mg ulipristal acetate, respectively; low-certainty evidence).[1] There may be little to no difference in bleeding reduction compared to ulipristal acetate 5 m (OR 0.71, 95% CI 0.30 to 1.68; 1 study, 199 participants; low-certainty evidence), and there is probably little to no difference in preoperative hemoglobin (MD −0.02, 95% CI −0.41 to 0.37; 242 participants; moderate-certainty evidence).[1] It is uncertain whether there is any difference in fibroid volume between GnRH analogs and cabergoline (MD 12.71 mL, 95% CI −5.92 to 31.34; 2 studies, 110 participants; I^2 = 0%; low-certainty evidence).[1] Adverse events such as hot flushes may be more likely with GnRH analogs (OR 2.83, 95% CI 1.68 to 4.77; 6 studies, 507 participants; I^2 = 59%; low-certainty evidence) compared to raloxifene, ulipristal, mifepristone, and cabergoline.[1]

In summary, pretreatment with GnRH analogs may reduce uterine and fibroid volume compared to placebo and other medical therapies (i.e., ulipristal, fulvestrant) and probably increases preoperative hemoglobin levels, but probably also increases the number of adverse events.[1] Blood transfusions and operation time during hysterectomy may be reduced, with fewer women experiencing postoperative morbidity.[1]

Cochrane Review: Gonadotropin-Releasing Hormone Agonists for Management of Endometriosis

A 2023 Cochrane Review assessed the effectiveness of GnRH agonists (goserelin, leuprolide, nafarelin, and triptorelin) in the treatment of painful symptoms associated with endometriosis.[2] Literature was searched through May 2022 for RCTs comparing GnRH agonists to progestogens, danazol, or placebo.[2] Seventy-two studies (n = 7355) met inclusion criteria.[2] The evidence was very low to low quality: the main limitations of all studies were serious risk of bias due to poor reporting of study methods, and serious imprecision.[2] Five RCTs used placebo as the comparator, 29 RCTs used danazol, 3 RCTs evaluated LNG-IUDs, 7 RCTs included oral or injectable progestogens, and the rest of the trials evaluated different dosing regimens of GnRH agonists.[2] No studies comparing GnRH agonists to analgesics were identified.[2]

In trials comparing GnRH agonists to placebo, GnRH agonists may decrease overall pain, reported as pelvic pain scores (risk ration [RR] 2.14; 95% CI 1.41 to 3.24, 1 RCT, n = 87, low-certainty evidence), dysmenorrhea scores (RR 2.25; 95% CI 1.59 to 3.16, 1 RCT, n = 85, low-certainty evidence), dyspareunia scores (RR 2.21; 95% CI 1.39 to 3.54, 1 RCT, n = 59, low-certainty evidence), and pelvic tenderness scores (RR 2.28; 95% CI 1.48 to 3.50, 1 RCT, n = 85, low-certainty evidence) after 3 months of treatment.[2] Treatment with GnRH agonists may be associated with a greater incidence of hot flushes compared to placebo at 3 months of treatment (RR 3.08; 95% CI 1.89 to 5.01, 1 RCT, n = 100, low-certainty evidence).[2]

For women treated with either GnRH agonists or danazol, the effects were not different on relief of overall pain using a visual analog scale (MD -0.30; 95% CI -1.66 to 1.06, 1 RCT, n = 41, very low-certainty evidence), pelvic pain (MD 0.20; 95% CI -0.26 to 0.66, 1 RCT, n = 41, very low-certainty evidence), dysmenorrhea (MD 0.10; 95% CI -0.49 to 0.69, 1 RCT, n = 41, very low-certainty evidence), dyspareunia (MD -0.20; 95% CI -0.77 to 0.37, 1 RCT, n = 41, very low-certainty evidence), pelvic induration (MD -0.10; 95% CI -0.59 to 0.39, 1 RCT, n = 41, very low-certainty evidence), and pelvic tenderness (MD -0.20; 95% CI -0.78 to 0.38, 1 RCT, n = 41, very low-certainty evidence) after 3 months of treatment.[2] For pelvic pain (MD 0.50; 95% CI 0.10 to 0.90, 1 RCT, n = 41, very low-certainty evidence) and pelvic induration (MD 0.70; 95% CI 0.21 to 1.19, 1 RCT, n = 41, very low-certainty evidence), the complaints may decrease slightly after 6 months of treatment with GnRH agonists, compared to danazol.[2]

The studies that compared GnRH agonists to LNG-IUDs found very low-certainty evidence for differences on effect on overall pain relief after 6 months of treatment (MD -0.76, 95% CI -1.62 to 0.10, I^2 = 22%, 3 RCTs, n = 58).[2] Seven studies were identified which compared GnRH agonists with oral or injectable progestogens, however, only one study reported relief of overall pain, after 3 months of treatment with either GnRH agonists or oral progestogens. There may be an improvement in overall pain, reported as pelvic pain (MD -2.50, 95% CI -3.55 to -1.45, 1 RCT, n = 261, low certainty of evidence) and dyspareunia (MD -2.10, 95% CI -2.83 to -1.37, 1 RCT, n = 261, low certainty of evidence) after 3 months of treatment, in favor of oral progestogens compared to GnRH agonists.[2] There may be a decrease of vaginal bleeding seen in women treated with GnRH agonists, compared to oral progestogens (RR 0.33, 95% CI 0.23 to 0.48, 1 RCT, n = 242, low certainty of evidence).[2] Also, there may be less weight gain in women treated with GnRH agonists instead of oral progestogens (RR 0.31, 95% CI 0.10 to 0.92, 1 RCT, n = 242, low certainty of evidence).[2]

In summary, for relief of overall pain, there may be a slight decrease in favor of treatment with GnRH agonists compared to placebo or oral or injectable progestogens.[2] The effects on alleviating pain are uncertain when comparing GnRH agonists with danazol or intra-uterine progestogens.[2] There may be a slight

increase in adverse effects when women are treated with GnRH agonists, compared to placebo.[2] Most of the evidence cited in this review was very low to low certainty due to a wide range of outcome measures and a wide range of outcome measurement instruments.[2]

Cochrane Review: Progestogens For Pain Symptoms Associated With Endometriosis

A 2025 Cochrane Review evaluated the harms and benefits of progestogens in the treatment of endometriosis-associated pain symptoms.[3] Literature was searched through October 2024 for RCTS that compared progestogens to placebo, other medications, or different progestogen doses.[3] Thirty-three RCTs (n=5,059) met inclusion criteria, 13 RCTs were assessed as having a low risk of bias.[3] Studies assessing the LNG-IUD were ineligible, as a separate Cochrane review assessed the evidence for this intervention.[44] The LNG-IUD Cochrane review found no high-quality evidence to support the use of LNG-IUD in management of endometriosis symptoms.[44]

Eight RCTs compared oral progestogens to placebo and determined oral progestogens probably reduce overall pain measured on a visual analogue scale (VAS; MD −2.58, 95% CI −3.13 to −2.03; moderate certainty), and probably reduce dysmenorrhea at 3 months (RR 0.21, 95% CI 0.07 to 0.70, moderate certainty), but may have little to no effect on pelvic pain at 3 months (RR 0.7, 95% CI 0.29 to 1.69; low certainty).[3] There is probably little to no difference between the interventions in study withdrawal due to adverse effects (RR 2.36, CI 0.74 to 7.52, moderate certainty) and cumulative side effects (RR 1.18, 95% CI 0.94 to 1.46, moderate certainty).[3]

Oral progestogens were compared with oral contraceptives in 4 RCTs and found no differences on improving pelvic pain measured on a VAS (MD 0.38, 95% CI −0.46 to 1.22, moderate certainty).[3] There was very low-certainty evidence about the effect of oral progestogens versus oral contraceptives on dysmenorrhea at 12 months (MD −0.57, 95% CI −1.29 to 0.15).[3] There may be little to no difference between oral progestogens and oral contraceptives in study withdrawal due to adverse effects (RR 0.75, 95% CI 0.27 to 2.07, low certainty), and there is probably little to no difference in cumulative side effects (RR 1.13, 95% CI 0.8 to 1.60, moderate certainty).[3]

Ten RCTs compared oral progestogens compared with GnRH agonists and showed very little or no difference on overall pain measured on a VAS (MD −0.01, 95% CI −0.30 to 0.28), risk of pelvic pain (RR 1.12, 95% CI 0.80 to 1.59), dysmenorrhea (RR 1.45, 95% CI 0.71 to 3.00), and study withdrawal due to adverse effects (RR 0.9, 95% CI 0.34 to 2.43).[3] All these outcomes had low-certainty evidence.[3] The risk of cumulative side effects was probably higher with oral progestogens (RR 1.44, 95% CI 1.11 to 1.86, moderate certainty) compared to GnRH agonists.[3]

In 2 RCTs comparing depot progestogens versus GnRH agonists, depot progestogens reduce dysmenorrhea risk slightly (RR 0.93, 95% CI 0.89 to 0.97, high certainty) but may have little to no effect on pelvic pain (RR 0.96, 95% CI 0.87 to 1.07, low certainty).[3] The interventions may be similar in study withdrawal due to adverse effects (RR 1.41, 95% CI 0.24 to 8.32, low certainty), but the risk of cumulative side effects is probably lower with depot progestogens (RR 0.03, 95% CI 0.01 to 0.11, moderate certainty).[3] One RCT compared depot progestogens to a GnRH antagonist and found depot progestogens may have little to no effect on pelvic pain (RR 0.85, 95% CI 0.7 to 1.03, low certainty), dysmenorrhea (RR 0.85, 95% CI 0.7 to 1.03, low certainty), and cumulative adverse effects (RR 1.04, 0.95 to 1.14, low certainty).[3] Study withdrawal due to side effects is likely higher with depot progestogens (RR 2.02, 95% CI 1.04 to 3.94, moderate certainty) compared to GnRH antagonists.[3]

In summary, in individuals with endometriosis, oral progestogens compared with placebo likely reduce overall pain and dysmenorrhea and may reduce pelvic pain.[3] Compared with other hormonal suppression strategies, the evidence is less certain due to the small number of studies for each comparison and outcome.[3]

After review, 13 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[45-50] wrong study design of included trials (e.g., observational),[51] comparator (e.g., no control or placebo-controlled),[52-57] or outcome studied (e.g., non-clinical).[58]

New Guidelines:
High Quality Guidelines:

Primary Dysmenorrhea Guidance
Society of Obstetrics and Gynecology Canada: Primary Dysmenorrhea
In May 2025 the SOGC issued guidance for management of primary dysmenorrhea.[4] Non-steroidal anti-inflammatory drugs are more effective than placebo but have more gastrointestinal side effects.[4] All currently available NSAIDs are of comparable efficacy and safety (high-quality evidence).[4] Dysmenorrhea responds favorably to the inhibition of ovulation. Combined hormonal contraceptives suppress ovulation and endometrial tissue growth, thereby decreasing menstrual blood volume and prostaglandin secretion with subsequent decreases in intrauterine pressure and uterine cramping.[4] Observational studies consistently demonstrate a lower prevalence of dysmenorrhea among individuals who use combined hormonal contraceptives.[4]
Specific recommendations include:

- Health care providers should offer NSAIDs or acetaminophen, administered with regular dosing regimens, as a as first-line treatment for most women unless contraindicated (strong recommendation, high-quality evidence).[4]
- Continuous or extended use combined hormonal contraceptives are recommended for the treatment of dysmenorrhea (strong recommendation, high-quality evidence).[4]

Uterine Fibroid Guidance
Canada's Drug Agency: Reimbursement Recommendation: Relugolix-Estradiol-Norethindrone for Uterine Fibroids
CDA published a review of relugolix combination therapy for management of uterine fibroids in August 2025.[5] The CDA has not been able to make a reimbursement recommendation for elagolix combination therapy in management of uterine fibroids as the manufacturer has not filed a submission with the agency. Evidence from 2 clinical trials demonstrated that more patients receiving relugolix combination therapy experienced a meaningful reduction in menstrual blood loss after being on treatment for 6 months compared to patients receiving placebo.[5] More patients receiving relugolix combination therapy had an improvement in anemia, pain, and health-related quality of life (HRQoL) compared to patients receiving placebo.[5] However, it is unclear if patients on the medication are able to avoid surgery over the long term.[5]

The committee reviewed the longer-term evidence from the extension studies that suggested treatment effects were maintained for reduced menstrual blood loss volume and patient-reported symptom severity and improved HRQoL (up to 104 weeks total treatment) and anemia based on hemoglobin levels (up to 52 weeks total treatment).[5] There were limitations with the study designs, a large number of discontinuations, and a potential selection bias for patients who respond to and tolerate the drug that increase the uncertainty of the longer-term results.[5] The CDA noted that clinical guidelines recommend nonhormonal drugs (NSAIDs, antifibrinolytics) or hormonal therapies (combined hormonal contraceptives, progestins, depot medroxyprogesterone and LNG-IUDs) for management of abnormal uterine bleeding in premenopausal women.[5]

- The CDA's Drug Expert Committee recommends that relugolix-estradiol–norethindrone acetate be reimbursed for the management of heavy menstrual bleeding associated with uterine fibroids in patients in the premenopausal stage only if these conditions are met:
    - Patients in the premenopausal stage and aged 18 years or older with confirmed uterine fibroids and heavy menstrual bleeding.[5]
    - The maximum duration of initial authorization is 6 months.[5]

- For renewal after initial authorization, the physician must provide proof of clinical response, defined as reduction in menstrual blood loss volume, reduction in pain, improvement in hemoglobin (in patients with anemia), or improvement in health-related quality of life.[5]
- Reimbursement for relugolix combination therapy should be discontinued upon occurrence of any of the following: successful surgery or procedure, plans for pregnancy, menopause, or a meaningful decline in BMD.[5]

National Institute for Health and Care Excellence: Relugolix–Estradiol–Norethindrone For Treating Symptoms Of Uterine Fibroids

NICE published guidance for the use of relugolix-estradiol-norethindrone combination therapy for treating moderate to severe symptoms of uterine fibroids in October 2022.[6] NICE guidance on heavy menstrual bleeding recommends that, when there is no identified cause and fibroids are less than 3 cm in diameter, pharmacological treatments include non-hormonal (tranexamic acid, non-steroidal anti-inflammatories) and hormonal medicines (LNG-IUD, combined hormonal contraception, cyclical oral progestogens).[6] If pharmacological treatment is unsuccessful or declined, or symptoms are severe, then surgical options (endometrial ablation, hysterectomy) are offered.[6] When fibroids are 3 cm or more in diameter, uterine artery embolization is another option before surgery.[6] Ulipristal acetate and myomectomy (a surgical option) are only considered if other surgical options and uterine artery embolization are unsuitable, declined or unsuccessful.[6] Pretreatment with injectable GnRH agonists before hysterectomy and myomectomy is considered if uterine fibroids are causing an enlarged or distorted uterus.[6] Relugolix combination therapy has shown to be effective in reducing menstrual blood loss volume associated with uterine fibroids compared to placebo.[6] There is no evidence directly comparing relugolix–estradiol–norethindrone acetate with GnRH agonists.[6]

- Relugolix–estradiol–norethisterone acetate is recommended as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age.[6]

Endometriosis Guidance

National Institute for Health and Care Excellence: Relugolix–Estradiol–Norethindrone For Treating Symptoms Of Endometriosis

In November 2024 NICE updated guidance for diagnosis and management of endometriosis.[59] No changes were made to first-line treatment recommendations which include a short-term trial (3 months) of acetaminophen or NSAIDs.[59] If first-line treatment is ineffective, hormonal treatment (the combined oral contraceptive pill or progestogen) should be offered to women with suspected, confirmed or recurrent endometriosis.[59] If medical treatment is not effective, GnRH antagonists are recommended as second line options. NICE has not developed guidance for the use of elagolix in managing symptoms of endometriosis but has issued guidance for the use of relugolix combination therapy. Clinical trial evidence shows that relugolix combination therapy reduces pain compared with placebo.[7] Relugolix combination therapy has not been directly compared in a clinical trial with usual treatment.[7] Indirect comparisons suggest that it is likely to reduce pelvic pain almost as well as GnRH agonists.[7] It is unclear how well relugolix-estradiol-norethindrone works compared with surgery.[7]

- Relugolix–estradiol–norethindrone is recommended as an option for treating symptoms of endometriosis in adults of reproductive age who have had medical or surgical treatment for endometriosis.[7]

European Society of Human Reproduction and Embryology: Endometriosis Guideline

The ESHRE guidance for management of endometriosis was updated in February 2022.[8] Treatment should begin with NSAIDs/analgesics and/or hormonal treatments (combined oral contraceptives, progestogens).[8] Second-line treatments include a GnRH agonist (i.e., leuprolide) or GnRH antagonists (i.e., elagolix, relugolix).[8] For the GnRH agonists, treatment is limited by their side effect profile and add-back therapy should be considered to prevent bone loss and hypoestrogenic symptoms.[8] Evidence is limited regarding GnRH antagonist dose or duration of treatment and the need for add-back therapy.[8] There are considerable side effects with GnRH antagonists, including the potential impact on bone density.[8] Aromatase inhibitors (i.e., letrozole, anastrozole) can be considered as second or third line treatment and must be combined with hormonal therapy in reproductive-aged women.[8] The guideline development group strongly believes that oral danazol should not be used unless no other medical therapy is available, due to its severe side effects (acne, edema, vaginal spotting,

weight gain, muscle cramps, deepening of voice, increase in facial hair).[8] For this reason, danazol is no longer recommended as a medical treatment for endometriosis associated pain in the current guideline.[8]

Strength of recommendations and quality of evidence are as follows:

- Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain (weak recommendation; very low-quality evidence).[8]
- It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists, or GnRH antagonists) as one of the options to reduce endometriosis-associated pain (strong recommendation; moderate-quality evidence).[8]
- It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain (strong recommendation; low-quality evidence).[8]
- It is recommended to prescribe GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (strong recommendation; low-quality evidence).[8]
- It is recommended that GnRH agonists and GnRH antagonists are prescribed as second-line (e.g., if hormonal contraceptives or progestogens have been ineffective) due to their side effect profile (good practice point based on clinical expertise).[8]
- Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms (strong recommendation; moderate-quality evidence).[8]
- It can be considered to prescribe GnRH antagonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (weak recommendation; moderate-quality evidence).[8]
- In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH antagonists, or GnRH agonists (strong recommendation; low-quality evidence).[8]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[60]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Goserelin	ZOLADEX	March 2023	Warnings/Precautions	Depression: Depression may occur or worsen in women receiving GnRH agonists. Monitor and manage appropriately.
Relugolix	ORGOVYX	March 2023	Warnings/Precautions	Relugolix is contraindicated in patients with severe hypersensitivity to relugolix or any of the product components. Hypersensitivity reactions, including pharyngeal edema and other serious cases of angioedema, have been reported in postmarketing in patients treated with relugolix.

				In the HERO study, patients treated with relugolix reported angioedema (0.2%). Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue relugolix and promptly seek medical care. Discontinue relugolix hypersensitivity reactions and manage as clinically indicated.
Triptorelin Pamoate	TRELSTAR	November 2023	Warnings/Precautions	Metabolic Syndrome: The use of GnRH agonists may lead to an increased risk of metabolic changes such as hyperglycemia, diabetes, hyperlipidemia, and non-alcoholic fatty liver disease. Monitor for signs and symptoms of metabolic syndrome including lipids, blood glucose level and/or HbA1c and manage according to institutional guidelines. Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in men. Monitor for cardiovascular disease and manage according to current clinical practice.
Triptorelin Pamoate	TRELSTAR	April 2024	Warnings/Precautions	Convulsions: Convulsions have occurred in patients treated with GnRH analogs with or without a history of predisposing factors. Manage patients who experience convulsions according to institutional guidelines.
Triptorelin Pamoate Goserelin Histrelin Leuprolide	TRELSTAR, TRIPTODUR ZOLADEX VANTAS, SUPPRELIN LUPRON, FENSOLVI, CAMCEVI, ELI	September 2025	Warnings/Precautions	Severe Cutaneous Adverse Reactions (SCARs), including Stevens Johnson syndrome/toxic epidermal necrolysis, occurred in patients treated with GnRH agonists. Interrupt treatment if signs or symptoms of SCARs develop. Permanently discontinue if SCARs are confirmed.
Leuprolide	LUPRON, FENSOLVI, CAMCEVI, ELIGARD	July 2023	Warnings/Precautions	Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors, and in patients on concomitant medications that have been associated with convulsions such as

				bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Patients receiving a GnRH agonist who experience convulsion should be managed according to current clinical practice.

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Appendix 1: HERC Guidance for Management of Dysmenorrhea and Pelvic Pain Syndrome

GUIDELINE NOTE 59, DYSMENORRHEA[9]

Line 551

Hysterectomy for dysmenorrhea may be indicated when all of the following are documented (A-G):

A) Patient history of:
   1) No treatable conditions or lesions found on laparoscopic examination
   2) Pain for more than 6 months with negative effect on patient's quality of life
B) Failure of a six-month therapeutic trial with both of the following (1 and 2), unless there are contraindications to use:
   1) Hormonal therapy (a or b):
      a) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
      b) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
   2) Nonsteroidal anti-inflammatory drugs
C) Evaluation of the following systems as possible sources of pelvic pain:
   1) Urinary
   2) Gastrointestinal
   3) Musculoskeletal
D) Evaluation of the patient's psychological and psychosexual status for nonsomatic cause of symptoms
E) Nonmalignant cervical cytology, if cervix is present
F) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
G) Negative preoperative pregnancy test unless patient is postmenopausal or has been previously sterilized

GUIDELINE NOTE 55, PELVIC PAIN SYNDROME[9]

Line 525

A) Diagnostic MRI may be indicated for evaluation of pelvic pain to assess for adenomyosis and to assist in the management of these challenging patients when all of the following are documented:
   1) Patient history of dysmenorrhea, pelvic pain or abnormal uterine bleeding for more than six months with a negative effect on her quality of life.
   2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
      a) Hormonal therapy (i or ii):
         i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
         ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
      b) Nonsteroidal anti-inflammatory drugs
   3) An endovaginal ultrasound within the past 12 months that shows no other suspected gynecological pathology if diagnostic MRI shows > 12mm thickening of the junctional zone, the presumptive diagnosis of adenomyosis is fulfilled. See Guideline Note 39.
B) Hysterectomy for chronic pelvic pain in the absence of significant pathology may be Indicated when all of the following are documented (1-7):

1) Patient history of:
    a) No treatable conditions or lesions found on laparoscopic examination
    b) Pain for more than 6 months with negative effect on patient's quality of life
2) Failure of a six-month therapeutic trial with both of the following (a and b), unless there are contraindications to use:
    a) Hormonal therapy (i or ii):
        i) Oral contraceptive pills or patches, progesterone-containing IUDs, injectable hormone therapy, or similar
        ii) Agents for inducing amenorrhea (e.g., GnRH analogs or danazol)
    b) Nonsteroidal anti-inflammatory drugs
3) Evaluation of the following systems as possible sources of pelvic pain:
    a) Urinary
    b) Gastrointestinal
    c) Musculoskeletal
4) Evaluation of the patient's psychological and psychosexual status for nonsomatic cause of symptoms
5) Nonmalignant cervical cytology, if cervix is present
6) Assessment for absence of endometrial malignancy in the presence of abnormal bleeding
7) Negative preoperative pregnancy test unless patient is postmenopausal or as been previously sterilized

Appendix 2: Current Preferred Drug List

GnRH Agonists

Generic	Brand	Route	Form	PDL
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	KIT	Y
histrelin acetate	SUPPRELIN LA	IMPLANT	KIT	N
leuprolide acetate	LUPRON DEPOT	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LEUPROLIDE DEPOT	INTRAMUSC	VIAL	N
leuprolide acetate	LUTRATE DEPOT	INTRAMUSC	VIAL	N
triptorelin pamoate	TRELSTAR	INTRAMUSC	VIAL	N
triptorelin pamoate	TRIPTODUR	INTRAMUSC	VIAL	N
nafarelin acetate	SYNAREL	NASAL	SPRAY	N
leuprolide acetate	LEUPROLIDE ACETATE	SUBCUT	KIT	N
histrelin acetate	SUPPRELIN	SUBCUT	KIT	N
leuprolide mesylate	CAMCEVI	SUBCUT	SYRINGE	N
leuprolide acetate	ELIGARD	SUBCUT	SYRINGE	N
leuprolide acetate	FENSOLVI	SUBCUT	SYRINGE	N
leuprolide acetate	LEUPROLIDE ACETATE	SUBCUT	VIAL	N

GnRH Antagonists

Generic	Brand	Route	Form	PDL
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix/estradiol/norethindrn	ORIAHNN	ORAL	CAP SEQ	N
relugolix/estradiol/norethindr	MYFEMBREE	ORAL	TABLET	N

Appendix 3 Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

Uterine Fibroids

1	elagolix.mp.	187
2	DANAZOL/	2383
3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Leiomyoma/	22103
11	9 and 10	394
12	limit 11 to (english language and humans and yr="2022 -Current")	50

Dysmenorrhea

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

1	elagolix.mp.	187
2	DANAZOL/	2383
3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Dysmenorrhea/	5156
11	9 and 10	74
12	limit 11 to (english language and humans and yr="2022 -Current")	11

Endometriosis

Ovid MEDLINE(R) ALL <1946 to January 05, 2026>

1	elagolix.mp.	187
2	DANAZOL/	2383

3	relugolix.mp.	225
4	Leuprolide/	3160
5	histrelin.mp.	137
6	Triptorelin Pamoate/	2056
7	Nafarelin/	327
8	Ethinyl Estradiol-Norgestrel Combination/	390
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	8454
10	Endometriosis/	28410
11	9 and 10	1250
12	limit 11 to (english language and humans and yr="2022 -Current")	45

Appendix 4: Key Inclusion Criteria

Population	Females
Intervention	GnRH agonists and antagonists
Comparator	Oral contraceptives, progestogens, danazol
Outcomes	Pain relief, improved quality of life, and for fibroids, amount of menstrual blood lost
Timing	6 months
Setting	Outpatient

Gonadotropin-Releasing Hormone Agonists

Goals:
- Restrict use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:
- Up to 6 months

Requires PA:
- All GnRH agonists

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 diagnosis funded by OHP?	**Yes:** Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3.

Approval Criteria		
3. Will the prescriber consider switching to a preferred product, if appropriate? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Go to #4
4. 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 #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is the diagnosis central precocious puberty or other endocrine disorder?	**Yes:** Go to #6	**No:** Go to #7
6. Is the prescriber a pediatric endocrinologist?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the diagnosis gender dysphoria?	**Yes:** Approve for 1 year	**No:** Go to #8
8. Is the patient of childbearing potential? ~~and pregnant or actively trying to conceive?~~	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Go to #10	**No:** Go to #11
~~9.~~10. 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 # 11	**No:** Pass to RPh. Deny; medical appropriateness.
~~10.~~11. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #12

Approval Criteria		
~~11.~~12. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	**Yes:** Approve for up to 3 months	**No:** Go to #13
~~12.~~13. Is this request for management of moderate to severe pain associated with pelvic pain or endometriosis in a woman ≥18 years of age?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
~~13.~~14. Has the patient tried and failed an adequate trial of at least 1 of the preferred endometriosis therapy options for at least 6 months including administration of combined hormonal contraceptives or progestins (oral, depot injection, ring, patch, implant, or intrauterine) alone? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the preferred therapy options?	**Yes:** Approve for 6 to 12 months, depending on selected medication. *Note maximum recommended duration of therapy for nafarelin and goserelin is 6 months. Leuprolide therapy should not exceed 12 months. If requesting continuation of therapy beyond FDA-approved duration, pass to RPh. Deny; medical appropriateness.	**No:** Go to #15 *Hormonal combination contraceptives or progestins do not require PA
~~14.~~15. RPh only: All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for conditions which are not outlined above is currently insufficient and should be denied for “medical appropriateness” If new evidence or guideline-recommendations are provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

P&T / DUR Review: *4/26 (DM); 8/23 (DM); 12/21 (DM); 3/19 (DM); 5/15*
Implementation: *9/1/23; 1/1/22; 5/1/19*

Gonadotropin-Releasing Hormone Antagonists

Goal(s):

- Promote safe use of elagolix and relugolix/estradiol/norethindrone in people with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).
- Promote use that is consistent with medical evidence and product labeling.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative lifetime treatment period not to exceed 24 months in patients with normal hepatic function. For patients with moderate hepatic impairment receiving 150 mg once daily, duration of therapy should not exceed 6 months. In patients receiving high dose elagolix therapy (200 mg twice daily), maximum treatment duration is 6 months.
- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

Requires PA:

- Elagolix (ORLISSA)
- Elagolix/estradiol/norethindrone (ORIAHNN)
- Relugolix/estradiol/norethindrone (MYFEMBREE)

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 therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3

Approval Criteria		
3. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this request for management of moderate to severe pelvic pain associated with endometriosis in a premenopausal patient?	**Yes**: Go to #6	**No:** Go to #12
6. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA- labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as combined hormonal contraceptives or progestins do not require PA
7. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine, gemfibrozil, etc.), combined P-glycoprotein inhibitor and moderate CYP3A inhibitor (e.g., erythromycin), combined P-glycoprotein inducer and strong CYP3A inducer (e.g., rifampin)? Note: Elagolix levels are increased when co-administered with OATP1B1 inhibitors. Relugolix levels are increased when co-administered with inhibitors such as erythromycin and decreased when co-administered with inducers such as rifampin. Avoid combinations of these therapies due to drug interactions that can increase the risk of adverse reactions or decrease the efficacy of GnRH antagonists.	**Yes:** Deny; medical appropriateness	**No:** Go to #8

Approval Criteria		
8. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months * FDA approved elagolix dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
11. Is the dose for elagolix 150 mg once daily or relugolix 40 mg /estradiol 1 mg/norethindrone 0.5 mg?	**Yes:** Approve for 6 months (cumulative lifetime treatment) * FDA approved elagolix dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the request for elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the patient tried and failed a trial of first line therapy options including at least 1 of the following for at least 6 months: a) hormone-releasing IUD OR b) continuous administration of combined hormonal contraceptives OR c) cyclic progestins OR d) tranexamic acid? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the first-line therapy options?	**Yes**: Go to #14	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as hormonal contraceptives, progestins, or tranexamic acid do not require PA
14. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months (cumulative, lifetime treatment)

Renewal Criteria		
1. Has the patient been receiving elagolix/estradiol/norethindrone for management of uterine fibroids or relugolix/estradiol/norethindrone for management of uterine fibroids or pain associated with endometriosis?	**Yes:** Go to #4	**No:** Go to #2
2. Has the patient been receiving therapy with elagolix 150 mg once daily for management of endometriosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
3. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #4
4. Has the patient's condition* improved as assessed and documented by the prescriber? *For endometriosis: has pain associated with endometriosis improved? For uterine fibroids: has patient experienced at least a 50% reduction in menstrual blood loss from baseline?	**Yes:** Approve for up to 18 months Document physician attestation received. Total cumulative treatment period not to exceed 24 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 4/26 (DM); 2/23(DM); 12/21, 3/19 (DM),11/18 (DE)
Implementation: 4/1/23; 1/1/22; 5/1/19

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

Orphan Drug Evaluation: Etuvetidigene autotemcel, suspension for intravenous use

Date of Review: April 2026
Generic Name: Etuvetidigene autotemcel

End Date of Literature Search: 02/13/2026
Brand Name (Manufacturer): WASKYRA

Dossier Received: No

Purpose for Review:

- To review evidence of safety and effectiveness of etuvetidigene autotemcel for people with Wiskott-Aldrich Syndrome.
- To establish prior authorization (PA) criteria to support medical appropriateness and necessity.
- Estimated wholesale acquisition cost (WAC) per member over 12 months: Not published as of 2/16/26; one-time gene therapy expected to cost over $1M.

Plain Language Summary:

- Wiskott-Aldrich Syndrome is a rare disease caused by a mutation or error in genes that are passed on by your parents. Most people with this condition are boys. They often do not have enough platelets and also have trouble fighting off infections. Platelets come from blood and help to stop bleeding when there is a cut or injury.
- People with Wiskott-Aldrich Syndrome often have itching, bleeding, and many infections. It is usually diagnosed during the first year of life. Some people have more symptoms than others.
- People with very severe symptoms may get a stem cell transplant, often as a child. This can cure the condition, but has many risks. People with less severe symptoms often are treated with supportive care for their lifetime. This can mean things avoiding certain sports which may cause injury and receiving blood transfusions for bleeding and medicines to treat infections such as antibiotics.
- People who do not have a donor for a stem cell transplant may be able to use a new medicine called gene therapy. Gene therapy can correct faulty genes to cure conditions like Wiskott-Aldrich Syndrome.
- In 2025, the Food and Drug Administration (FDA) approved a new medicine called etuvetidigene autotemcel (WASKYRA). It is a gene therapy to treat Wiskott-Aldrich Syndrome in people who are at least 6 months old who do not have a donor for a stem cell transplant.
- Twenty-seven people with Wiskott-Aldrich Syndrome who received etuvetidigene autotemcel had a decrease in the number of infections and bleeding episodes after having gene therapy, compared to the year before having gene therapy.
- The Drug Use Research and Management group recommends that the Oregon Health Authority only pay for etuvetidigene autotemcel when patients have a severe form of the disease which cannot be managed by supportive care, cannot have a donor stem cell transplant because there is no appropriate donor, and are healthy enough to tolerate conditioning therapy required to receive the medicine.

Research Questions:

Author: Sara Fletcher, PharmD, MPH, BCPS

1. What is the effectiveness and safety of etuvetidigene autotemcel for the treatment of Wiskott-Aldrich Syndrome (WAS)?
2. Are there subpopulations based on age and symptom severity for which etuvetidigene autotemcel is more effective or safe?

Conclusions:

- There is low quality evidence from the composite results from the combined results of 2 single-arm, open-label studies and use from expanded access programs (N=27) of people with WAS. These studies showed a reduction of severe infections 6 to 18 months after gene therapy when compared with the 12 months prior to treatment (Before treatment 2.0 infections per patient per year; 95% confidence interval [CI] 1.5 to 2.61; After treatment 0.2 infections per patient per year; 95% CI 0.04 to 0.4). There was also a reduction in the rate of moderate to severe bleeding episodes in the same time period (Before treatment 2.0 events per patient per year; 95% confidence interval [CI] 1.5 to 2.61; After treatment 0.8 infections per patient per year; 95% CI 0.49 to 1.22).[1-3]
- There is no randomized controlled data on the use of etuvetidigene autotemcel compared to supportive care of other treatments.[1]
- One patient died during follow up from deterioration of a pre-existing neurological condition. There were 45 serious adverse reactions in 21 patients. Most were infectious including catheter related (59%), respiratory tract infection (67%) and conjunctivitis (37%).[1] Patients are required to undergo myeloablation prior to gene therapy infusion.
- There is no data on use in less severe disease forms such as x-linked thrombocytopenia (XLT). There is insufficient evidence for use of etuvetidigene autotemcel in other conditions.

Recommendations:

- Implement prior authorization criteria for use of etuvetidigene autotemcel.

Background:

- Wiskott-Aldrich syndrome is a rare, X-linked disease resulting from WAS gene mutation which alters Wiskott-Aldrich syndrome protein (WASp) expression.[4] There are over 300 identified WAS gene mutations and these may result in different WASp expression, which may vary disease severity.[5] Absence of WASp expression, or classic WAS, is likely to result in severe disease while partial WASp expression may result in varying phenotypes, including milder disease forms such as XLT, which can affect females and may have similar bleeding but lacks other significant clinical features and can be managed with conservative supportive care.[4,5] Mutations can be divided into Class I and Class II mutations, where Class I often have better long-term survival, but both mutation types can develop severe complications from bleeding and infections.[3]
- Patients are often diagnosed with WAS as infants and young children presenting with eczema, thrombocytopenia, and recurrent infections due to immunodeficiency.[4] These patients are at higher risk of autoimmune diseases and certain types of cancers, especially non-Hodgkin lymphomas and leukemias as they get older.[3] Prognosis for those with severe disease without definitive therapy is survival up to 14.5 years. Premature death is due to severe infections, hemorrhage, and malignancies.[3] Prognosis worsens with the development of autoimmune or malignant complications.[3]
- Scoring systems exist to quantify severity and predict patients who may benefit from early definitive therapy.[3,5,6] The WAS clinical score **(Appendix 2)**, also called the Zhu scoring system, ranges from 0 to 5; scores of 3 or greater represent severe versions of the disease and correlate with absence of WASp expression and more severe pathogenic gene variants.[3]
- Mild and moderate versions of the disease, including XLT, are generally treated with supportive care to manage eczema, thrombocytopenia, and recurrent infections.[4] Severe presentations of WAS are generally referred for definitive therapy of hematopoietic stem cell transplantation (HSCT) with a

matched donor when available. Recent approval of gene therapy offers another definitive therapy option for those without a HSCT matched donor option.[4]

- Estimated frequency of diagnosis:
  - Incidence estimates vary from 1:50,000-250,000 live births, and 1-4 per million male live births.[4,5]
  - In Oregon Medicaid, 6 fee-for-service (FFS) and coordinated care organization (CCO) members had medical claims with the diagnosis of WAS (ICD-10 code of D82.0) from 04/01/2024 to 03/31/2025. Estimates may be inflated as the milder disease version of XLT often uses the same code and the patient count includes both male and female patients. Most of these members have claims indicating previous history of HSCT.
- Diagnostic Criteria: Diagnosis should be confirmed by genetic testing for deleterious WAS mutations and/or assessment of abnormal WASp expression in addition to clinical signs and symptoms.[4]
- Outcome Assessments: One time gene therapy with no renewal criteria needed. Survival and reduction of sequelae of WAS (e.g., bleeding, infections, eczema) should be monitored by clinical team.

Drug Information

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

Etuvetidigene autotemcel is prepared by collecting the patient's own hematopoietic stem cells, genetically modifying these cells to carry the WAS gene with an HIV-1 based lentiviral vector, then re-infused after myeloablation with rituximab, busulfan, and fludarabine.[1]

Clinical Efficacy and Safety:

Clinical trials used to support FDA approval are described and evaluated below in **Table 1**. Noteworthy trial design and patient characteristics include:

- Data for efficacy and safety are derived from 2 clinical studies and patients from an expanded access program (EAP). An interim analysis of study 1 (NCT01515462) has been published, while all remaining information is derived from the package insert and FDA review materials. Full assessment of data and risk of bias is not possible.
- Trial duration: At time of FDA analysis 8 of 27 patients had at least 8 years follow up, 1 of 27 died and had less than one year follow up, and the remaining patients had between 1 and less than 8 years follow up since treatment. Range of 1.2 to 13.3 years follow-up was documented for the surviving 26 patients.
- Number of participants: NCT01515462 n=8, NCT03837483 n=10, EAP n=9[1]
- Comparator: 12-month pre-treatment outcomes which were collected retrospectively and have irreconcilable data issues including missing data.[2]
- Key inclusion criteria: Wiskott-Aldrich Syndrome with WAS genetic mutation AND absent WASp expression or severe WAS mutation[3,7] or severe clinical phenotype (Zhu clinical score $\geq$3); no human leukocyte antigen (HLA)-identical sibling donor OR if under 5 years old with no suitable 10/10 matched unrelated donor or 6/6 unrelated cord blood donor.[1,6]
- Key exclusion criteria: human immunodeficiency virus (HIV) infection; neoplasia; cytogenetic alterations typical of myelodysplastic syndrome or acute myeloid leukemia; end-organ damage; previous allogeneic HSCT in previous 6 months or earlier but had evidence of residual cells of donor origin.[1,6]
- Baseline disease severity and population characteristics: All had severe disease (Not XLT) based on inclusion criteria.
  - Median age 2.6 years and most patients under 18 years old.

- All patients had thrombocytopenia, most patients had some form of eczema (85.2%).
- WAS clinical score 3 or greater in almost all patients (92.6%) and most had a severe WAS mutation (81%).

- Setting: All patients treated at single site in Italy except one patient received treatment in the United States.
- Magnitude of benefit and clinical relevance of results: Data derived from safety collection procedures of early phase 1/2 studies without prespecified efficacy hypothesis tests. FDA statistical review deferred to clinical team to assess overall benefit-risk assessment based on considerations of unmet clinical need.[2]
- Safety signals: Etuvetidigene autotemcel has been studied in 27 patients with median follow-up of 5.67 years (range 0.37 to 13.26 years).[1] There were 45 serious adverse events which occurred in 21 patients (78%) including catheter-related infection, bacterial, viral, and fungal infections, pyrexia, prolonged neutropenia, vomiting, and veno-occlusive disease.[1] A list of warnings and precautions related to treatment is listed in **Appendix 1**. Drug interactions include anti-retroviral medication which may interfere with manufacturing process.[1]
- Subgroup analyses: Small sample size precludes ability to assess subgroups beyond inclusion/exclusion criteria which might have more benefit from therapy.

See **Table 1** for major evidence limitations including:

- Single-arm, open-label study design, inclusion of non-study patients for composite results, with retrospective accumulation of historic comparative data results in high risk of selection, performance, and detection bias. Unclear risk of reporting and other bias with low risk of attrition bias.
- Some applicability concerns given single treatment center outside of United States healthcare system with less ethnic diversity. Results only applicable to patient with severe disease as defined by trial and given significant risks of myeloablation should be used specifically in WAS population with highest chance of benefit due to more significant disease or poor prognosis disease based on genetic testing, WASp expression, and clinical scoring.

Table 1. 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. Package Insert[1] and FDA Review documents[2,3] Study 1 NCT01515462 Ferrua et al[6] (interim analysis after 8 patients having 3.6 y median follow-up [range 0.5-5.6]) Open-label,	1. Autologous CD34+ cells genetically modified with a lentiviral vector encoding for human WAS cDNA *after* rituximab, busulfan, and fludarabine conditioning. Study 1: Fresh formulation of gene therapy Study 2: cryopreserved	Demographics: - Median age: 2.6 years; range 11mo-35y; 2/27 over 18 years. - Male: 100% - Race White: 74% Asian: 15% Black: 7% Thrombocytopenia: 100% -Eczema: 85.2% (range transient to severe) -Zhu score ≥3: 92.6%	ITT: 27 PP: 26 Attrition: 1 (mobilization failure and death)	Primary Endpoint: Severe infections 6-18 months after infusion vs. 12 month pre-treatment period 1. Before: 2.0 (95% CI 1.5 to 2.61) infections per patient per year 2. After: 0.2 (95% CI 0.04 to 0.40) infections per patient per year Rate of moderate-severe bleeding episodes in the 12 months after period vs. pre-treatment period	NA for all	Serious adverse events: 21 (78%); 45 events total Death 1 (3.7%) 35 yo at age of treatment due to deterioration of pre-existing neurological condition.	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Unrandomized, single-arm design Performance Bias: (High) Single-arm design, analysis included summation from study and non-study participants Detection Bias: (High) Not designed originally for efficacy testing, historic comparative data component implemented *post hoc* with retrospective and incomplete data collection.[2] Attrition Bias: (Low) Surviving patients followed long term post-treatment. Reporting Bias: (Unclear) Full published protocol was not located, full results unpublished. Other Bias: (Unclear) Funding by Italian Telethon Foundation, GlaxoSmithKline, and Orchard Therapeutics.

single-arm, single-center study, phase 1/2 Study 2 NCT03837483 Open-label, single-arm, multicenter study Early Access Program Enrollments occurred between April 2010 and March 2022.	formulation of gene therapy	-Severe mutation: 81% Key Inclusion Criteria: - Genetically confirmed WAS diagnosis - Severe symptoms (Zhu clinical score ≥ 3) OR Severe WAS mutation OR Absent WASp expression - No appropriate sibling, unrelated, or cord blood donor. Key Exclusion Criteria: - Allogenetic hematopoietic stem-cell transplant within 6 months or evidence of residual cells of donor origin - Prior gene therapy - HIV infection - -neoplasia - Cytogenetic alterations of myelodysplastic syndrome or AML		1. Before: 2.0 (95% CI 1.5 to 2.61) events per patient per year 2. After: 0.8 (95% CI 0.49 to 1.22) events per patient per year				**Applicability**: Patient: Rare disease affecting primarily male population. Patient population all from Italy and limited inclusion of Black or Hispanic patients. Potential differences in health system and supportive care from United States. Intervention: Varied between studies given dose finding phase 1/2 design and transition from fresh to cryopreserved formulation. Comparator: Historic comparison often used in rare disease single-arm studies, but should be collected as part of *a priori* protocol. Outcomes: Appropriate given complications of WAS. Setting: Single treatment site in Italy except one patient was treated in United States.

Abbreviations: AML = acute myeloid leukemia; ARR = absolute risk reduction; CI = confidence interval; HIV = human immunodeficiency virus; ITT = intention to treat; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; WAS = Wiskott-Aldrich syndrome; WASp =Wiskott-Aldrich syndrome protein; yo = years old; y = years.

References:

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Appendix 1: Prescribing Information Highlights

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

WASKYRA (etuvetidigene autotemcel) suspension, for intravenous use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
WASKYRA is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. (1)

----------DOSAGE AND ADMINISTRATION----------
For autologous use only. For intravenous use only.
- Patients are required to undergo hematopoietic stem and progenitor cell (HSPC) mobilisation followed by apheresis to obtain $CD34^+$ cells for WASKYRA manufacturing. (2.2)
- Dosing of WASKYRA is based on the number of $CD34^+$ cells in the infusion bag(s) per kg of body weight at the time of infusion. (2.1)
- The minimum recommended dose is 7×10^6 $CD34^+$ cells per kg.
- Reduced-intensity conditioning is required before infusion of WASKYRA. (2.2)
- Prior to WASKYRA infusion, confirm that the patient's identity matches the essential unique patient information on the infusion bag(s). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
WASKYRA is packaged in one to eight infusion bags overall containing a suspension of $2–11.4 \times 10^6$ cells /mL ($1.9–11.4 \times 10^6$ $CD34^+$ cells/mL) in a cryopreservative solution. (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to the active substance or to any of the excipients. (4)
- Previous treatment with HSCT within 6 months prior to screening or HSCT with evidence of residual donor cell. (4)
- Previous treatment with hematopoietic stem cell gene therapy. (4)
- Contraindications to the mobilization and the conditioning regimen. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity and infusion-related reactions: Monitor patients for hypersensitivity and infusion-related reactions during and after infusion. (5.1)
Engraftment failure: Monitor patients for signs and symptoms of engraftment failure. In case of engraftment failure, infuse the non-transduced back-up hematopoietic stem cells according to local standards. (5.2)
Cytopenias: Severe cytopenias, including anemia, neutropenia, and thrombocytopenia have occurred for several weeks following reduced intensity conditioning and WASKYRA infusion. Monitor patients for signs and symptoms of cytopenia for at least 8 weeks after treatment with WASKYRA and manage accordingly. (5.3)
Serious infections: Serious infections have occurred with WASKYRA administration. Increased susceptibility to infections may occur due to concomitant administration of rituximab and conditioning regimen. Monitor patients for signs and symptoms of infection before and after WASKYRA infusion and treat appropriately. (5.4)
Transmission of an infectious agent: All infections thought to be transmitted by WASKYRA should be reported to Fondazione Telethon ETS at 1- 888- 212- 6928. (5.5)
Hepatic veno-occlusive disease: Monitor patients for signs and symptoms of veno-occlusive disease including assessment of liver function tests for one month after WASKYRA infusion (5.6)
Risk of oncogenesis: There is a lifelong risk of lentiviral vector (LVV)-mediated insertional oncogenesis and secondary malignancy after treatment with WASKYRA. Monitor patients after treatment with WASKYRA for the development of malignancies. (5.7)
Interference with HIV testing: Patients who have received WASKYRA may test positive by polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion, resulting in a false positive test for HIV. Do not screen patients who have received WASKYRA for HIV infection using a PCR-based assay. (5.8)
Blood, organ, tissue and cell donation: Patients treated with WASKYRA should not donate blood, organs, tissues and cells for transplantation at any time in the future. (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥ 20%) are catheter related infections, bacterial and viral infections, diarrhea, vomiting, stomatitis, liver injury, head injury, rhinitis, cough, rash, petechiae, hypersensitivity, anemia, febril neutropenia, epistaxis, pyrexia, catheter site complications.(6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fondazione Telethon ETS at toll-free phone 1-888-212-6928 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2025

Appendix 2: Wiskott-Aldrich Syndrome Clinical Scoring System (Zhu Scoring system)[3]

Clinical Scores	XLT 0.5	XLT 1	XLT 2	WAS 3	WAS 4	WAS 5A	WAS 5M
Thrombocytopenia	+/-	+	+	+	+	+	+
Eczema	-	-	+/-	+	++	++/-	++/-
Immunodeficiency	-	-	+/-	+	++	++/-	++/-
Autoimmunity	-	-	-	-	-	+	-
Malignancy	-	-	-	-	-	-	+
Abbreviations: WAS = Wiskott-Aldrich Syndrome; XLT = X-linked Thrombocytopenia.							

Etuvetidigene autotemcel (WASKYRA)

Goal(s):
- Limit to populations which have been studied and approved by the Food and Drug Administration
- Promote evidence-based standard of care in patients diagnosed with severe Wiskott-Aldrich Syndrome.

Length of Authorization:
- One time dose (authorization one year to allow for coordination of care)

Requires PA:
- Etuvetidigene autotemcel

Covered Populations: FFS and CCO patients beginning 02/01/2026 (provider administered claims)

Covered Alternatives:
- No covered alternatives
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved age and indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug prescribed by a specialist with experience treating Wiskott-Aldrich Syndrome (e.g., clinical geneticist, pediatric hematologist, pediatric infectious disease specialist)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there documentation of genetically confirmed Wiskott-Aldrich Syndrome (e.g. mutation of the WAS gene)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is severe Wiskott-Aldrich Syndrome or poor prognosis documented by any of the following: • Wiskott-Aldrich Syndrome Clinical Score (Zhu Score) of 3 or higher OR • A severe mutation (e.g., nonsense, frame shift caused by deletions or insertions, splicing defects) OR • Absent Wiskott-Aldrich Syndrome protein (WASp) expression (e.g., <5% of lymphocytes expressing WASp)	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical necessity
6. Is there documentation that there is no suitable human leukocyte antigen (HLA)-matched related stem cell donor available?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation that the patient does not have a contraindication to therapy? Contraindications include: • Hypersensitivity to the active substance or any of the excipients • Previous hematopoietic stem cell transplant (HSCT) within 6 months prior to screening or HSCT with evidence of residual donor cells • Previous hematopoietic stem cell gene therapy • Contraindications to the mobilization and conditioning (myeloablation) regimen	**Yes**: Pass to RPh; Pend. Refer to DMAP for secondary review. If approved after secondary review, approve one (lifetime) dose with 1 year duration to allow for care coordination.	**No:** Pass to RPh. Deny; medical appropriateness

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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Orphan Drug Evaluation: Myalept® (metreleptin) subcutaneous injection

Date of Review: April 2026
Generic Name: metreleptin

End Date of Literature Search: 01/16/2026
Brand Name (Manufacturer): MYALEPT (Chiesi)

Dossier Received: Yes

Purpose for Review:

- To review evidence of safety and effectiveness of metreleptin in people with lipodystrophy due to leptin deficiency and to establish prior authorization (PA) criteria to support medical appropriateness and necessity for metreleptin.

Plain Language Summary:

- Lipodystrophy (also called fat redistribution) is a rare condition that affects how the body stores fat. Some people with lipodystrophy do not have enough leptin, a hormone that affects appetite and energy use. Diabetes, liver disease, and high blood triglyceride levels are linked to having low levels of leptin.
- Diet, exercise, and medicines that manage diabetes (insulin, metformin) and high triglycerides (fibrates, statins) are the current preferred treatments for people with lipodystrophy.
- Metreleptin mimics the effects of leptin in the body and is approved by the Food and Drug Administration (FDA) in people who have low levels of leptin and generalized lipodystrophy (either the inherited or acquired form). Metreleptin is injected under the skin (subcutaneously) once a day.
- Metreleptin is not approved for use in people with human immunodeficiency virus (HIV)-related lipodystrophy or serious liver disease.
- Side effects with metreleptin include headaches, feeling tired, low blood sugar, decreased weight, stomach pain, and nausea. Metreleptin has been linked to a certain type of cancer called T-cell lymphoma and is only available through the manufacturer's restricted safety program.
- The recommendation for the Oregon Health Plan is that metreleptin be covered for people diagnosed with generalized lipodystrophy due to low leptin levels and when other treatments have been prescribed to treat diabetes and high triglycerides.

Research Questions:

1. What is the efficacy and safety of metreleptin in people with generalized lipodystrophy?
2. Are there populations based on demographic characteristics (e.g., age), symptom severity, type of lipodystrophy for which metreleptin is more effective or safe?

Conclusions:

- The clinical trial that supported FDA approval is not published, but study details are included in the prescribing information.[1]
- A phase 2 study evaluated metreleptin dosing and the subsequent open-label, single site, long-term extension study (n=66) conducted over 14 years provides evidence for the safety and efficacy of metreleptin in treating patients with congenital or acquired generalized lipodystrophy due to leptin

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deficiency.[2] The co-primary efficacy endpoints were change in HbA1c and percent change in fasting serum triglycerides from baseline to 12 months. Metreleptin treatment led to a reduction in mean hemoglobin A1c (HbA1c) at 12 months, from 8.6% at baseline to 6.4% (95% Confidence interval [CI] not reported; p<0.001), and mean fasting triglycerides decreased from 1,302 mg/dL at baseline to 398 mg/dL at 12 months (95% CI not reported; p<0.001); (low-quality evidence for both endpoints).[2]

- The most common adverse events included: weight decrease (26%), abdominal pain (17%), hypoglycemia (15%), headache (12%) and decreased appetite (12%).[2] The label for metreleptin carries two black boxed warnings: 1) T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, in those both treated and untreated with metreleptin, and 2) anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with metreleptin.[1]
- Metreleptin has been studied in patients with partial lipodystrophy but has not received FDA approval for use in this population because the results did not show efficacy in reducing HbA1c and triglycerides.[1,3] Patients with HIV-related lipodystrophy, non-alcoholic steatohepatitis (NASH) and obesity or metabolic disease not associated with leptin-deficient lipodystrophy are also not approved for metreleptin therapy.[1]

Recommendations:

- Implement prior authorization proposed in **Appendix 2** to ensure standard of care in patients diagnosed with lipodystrophy due to leptin deficiency.

Background:

Leptin is a naturally occurring hormone predominantly secreted by adipose tissue that plays a central role in the neurohormonal regulation of energy homeostasis and fat and glucose metabolism.[4] Lipodystrophy syndromes due to leptin deficiency are rare diseases of the adipose tissue characterized by a complete or selective deficiency of body fat.[5] Instead of being stored in adipocytes, lipids are stored in the liver and muscles which results in diabetes, insulin resistance, and metabolic comorbidities (e.g., hepatic steatosis, hypertriglyceridemia).[5] The lack of leptin can lead to hyperphagia (constant hunger) which also contributes to metabolic abnormalities.[5] The lipodystrophy syndrome can be classified as autoimmune (acquired) or congenital, and subclassified based on the extent of fat pattern loss as generalized or partial.[5] Acquired lipodystrophies are associated with immunological abnormalities including dermatomyositis, autoinflammatory disorders, tissue specific autoimmunity, and myeloid disorders (e.g. myelosuppression and lymphoma).[4] Generalized lipodystrophy is usually associated with very low levels of leptin and severe metabolic disease; partial lipodystrophy is associated with a range of leptin levels and may or may not be accompanied by metabolic disease.[4] Complications of lipodystrophy include multi-organ damage affecting the heart, liver, kidneys and pancreas, leading to high morbidity and premature death.[6]

- Diagnosis of lipodystrophy is based on history, physical examination, body composition, and metabolic status.[6] There are no defined serum leptin levels that establish or rule out diagnosis of lipodystrophy.[6]
- Standard of care for leptin-deficient lipodystrophy includes a balanced diet (50-60% carbohydrates, 20-30% fat, and 20% protein), exercise, and pharmacological treatment of diabetes (insulin, metformin) and hyperlipidemias (fibrates, statins).[6]
- The prevalence of lipodystrophy depends on the subtype but overall is around 2.5 per 1 million of the overall population.[7] Generalized lipodystrophy has an estimated prevalence of 0.23 to 0.96 people per million and partial lipodystrophy has an estimated prevalence of 1.67 to 2.84 people per people per million.[8] Acquired generalized lipodystrophy is more common in females than males (3:1 ratio) and usually appears before adolescence.[6]
- In the Oregon Health Plan, 62 people had a diagnosis of lipodystrophy in the past year. Most of the patients (n=53) are enrolled in a Coordinated Care Organization (CCO) and 5 patients are enrolled in fee-for-service (FFS).

- Metreleptin is a recombinant analog of leptin and differs by one amino acid compared with native human leptin.[4] Metreleptin dosing is based on weight and gender. Gender dimorphism of leptin levels has been identified in healthy subjects, with women having higher leptin levels than men even after adjustment for differences in body composition.[4]
- Metreleptin is the only medication approved by FDA as an adjunct to diet as replacement therapy in patients with congenital or acquired generalized lipodystrophy due to leptin deficiency.[1] According to FDA, the effectiveness of metreleptin for the treatment of metabolic complications of partial lipodystrophy have not been established.[1]
- The annual wholesale acquisition cost (WAC) for metreleptin is $6,695 per 11.3 mg vial. Since the dosing is weight-based, the cost may vary depending on the dose the patient is prescribed ranging from one vial per day to one vial every 3 days. The annual cost could range from 0.8 to 2.4 million dollars.
- Canada's Drug Agency (CDA)[8] and the National Institute for Health and Care Excellence (NICE)[7] have evaluated the safety and efficacy of metreleptin in leptin-deficient lipodystrophy patients.
    - CDA recommends metreleptin as an adjunct to diet as replacement therapy when prescribed by an endocrinologist to treat complications of leptin deficiency in lipodystrophy patients:
        - with confirmed congenital generalized lipodystrophy (Berardinelli-Seip syndrome) or acquired generalized lipodystrophy (Lawrence syndrome) in adults and children 2 years of age and older with at least one metabolic abnormality of diabetes, insulin resistance, or high levels of triglycerides: OR
        - with confirmed familial partial lipodystrophy or acquired partial lipodystrophy (Barraquer-Simons syndrome) in adults and children aged 12 years and older with persistent significant metabolic disease for whom standard treatments for a 12-month period have failed to achieve adequate metabolic control, defined as hemoglobin A1c (HbA1c) higher than 6.5% or fasting triglycerides higher than 5.65 mmol/L (101.8 mg/dL).[8]
        - Patients should not be pregnant, lactating, or have HIV-associated lipodystrophy.[8]
        - Maximum duration of initial authorization is 12 months.[8]
        - Renewal after initial authorization requires documentation of beneficial metabolic effect defined as:
            - HbA1c reduction of at least 0.5% from baseline; or
            - Reduction of fasting triglycerides by at least 15% from baseline.[8]
    - NICE guidance recommends metreleptin as an option for treating complications of leptin deficiency in lipodystrophy for:
        - People who are 2 years of age and have generalized lipodystrophy.
        - People who are 12 years of age with partial lipodystrophy do not have metabolic control despite standard treatments. Metreleptin is only recommended if the HbA1c level is higher than 7.5% or fasting triglycerides higher than 5.0 mmol/L (90 mg/dL).[7] (The European Medicines Agency (EMA) label for metreleptin includes people aged 12 years and older with partial lipodystrophy.[6])

Drug Information

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

Clinical Efficacy and Safety:
The clinical trial that supported FDA approval is not published, but study details are included in the prescribing information. The published clinical trial to support the safety and efficacy of metreleptin is described and evaluated in **Table 1**.

Noteworthy trial design and patient characteristics include:

- Long-term Extension Trial Duration: 14 years
- Number of Participants: 66 adults and children
- Comparator: Single-arm study at one site. There are no trials that compare metreleptin with standard supportive care.
- Baseline disease severity and population characteristics:
    - Most of the patients were female (77%) and the median age was 15 years.[2]
    - The majority of patients had congenital lipodystrophy (68%), while 21% had acquired lipodystrophy.[2]
    - The mean baseline HbA1c was 8.6% and the fasting triglyceride level was 1,284 mg/dL.[2]
    - Eighty percent of patients were taking diabetic medications and 52% were taking lipid-lowering medications.[2]

Efficacy:

- Co-primary efficacy endpoints: Change in HbA1c and percent change in fasting serum triglycerides from baseline to 12 months.
- Metreleptin treatment led to a 2.2% mean reduction in HbA1c at 12 months from 8.6% at baseline to 6.4% (95% CI not reported; $p<0.001$) and fasting triglycerides decreased from a mean of 1,302 mg/dL at baseline to a mean of 398.6 mg/dL at 12 months (95% CI not reported; $p<0.001$).[2]

Safety:

- Adverse Effects:
    - Most common adverse events included: weight decrease (26%), abdominal pain (17%), hypoglycemia (15%), headache (12%), and decreased appetite (12%).
    - Ten patients (15.2%) developed a neoplasm during the study; one case of anaplastic large-cell lymphoma was assessed as treatment-related.[2]
- The label for metreleptin carries a boxed warning that T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, in those both treated and untreated with metreleptin.[1] Patients with acquired generalized lipodystrophy appear to be at a higher risk for lymphoma than the general population, likely due to underlying autoimmunity.[2] In addition, a second boxed warning notes that anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with metreleptin.[1] The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of metreleptin efficacy.[1] Worsening metabolic control and severe infection have been reported.[1] The manufacturer recommends testing for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of efficacy during metreleptin therapy.[1]
- Metreleptin is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and the risk of lymphoma.[1]

Other Populations:
Metreleptin is not approved to treat partial lipodystrophy, HIV-related lipodystrophy, NASH, obesity, or metabolic disease not associated with leptin-deficient lipodystrophy.[1]

See **Table 1** for major evidence limitations including:

- Single-arm, open label study design in small number of patients with generalized lipodystrophy, a rare condition. Population was mostly female, which reflects prevalence of the condition.
- Large number of dropouts and missing data. Last observation carried forward (LOCF) imputed for missing results that were 6 months post baseline assessments.
- Primary efficacy outcomes surrogate metabolic endpoints: change from baseline in HbA1c and fasting triglycerides. No evidence from this study that metreleptin helps improve hyperphagia or health-related quality of life.

Table 1. 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. Brown RJ, et al.[2] Phase 2 Pilot: NCT00005905 Phase 3 Extension: NCT00025883 Open-label, single-arm, single-center study	1. Metreleptin SC 0.08 to 0.10 mg/kg/day in females aged 5 years and older; 0.06 mg/kg/day in all males and females aged less than 5 years. Dose could be increased in increments of 0.02 mg/kg/day in females aged ≥ 10 yo and 0.01 mg/kg/day in all other patients. Dose capped at 0.24 mg/kg/day.	Demographics: -Congenital LD: n = 45 -Acquired LD: n = 21 -Mean fasting leptin: 1.3 ng/mL -Mean baseline HbA1c: 8.6% -Mean fasting TG: 1,284 mg/dL -Mean FPG: 185.6 mg/dL -Female: 77% -Median Age: 15 yrs -Race: --White: 47% --Black: 24% --Hispanic: 17% --Asian: 4.5% --Native American: 3% -Taking diabetic medications: 80% -Taking lipid-lowering medications: 51.5% Key Inclusion Criteria: -Aged 6 mos and older -Diagnosis of LD -Serum leptin < 12 ng/mL (females) and < 8 ng/mL (males) -At least one metabolic abnormality:	ITT: 66 PP: 43 Attrition: 23 (35%)	Co-primary Endpoints: Change from baseline in mean HbA1c and mean fasting TG levels at 12 months. n = 59 Baseline HbA1c: 8.6% HbA1c at 12 mos: 6.4% Mean change: -2.2% (95% CI NR; p<0.001) n = 57 Baseline fasting TG: 1,302 mg/dL Fasting TG at 12 mos: 398.6 mg/dL Mean change: -69% (95% CI NR; p<0.001) Secondary Endpoint: Mean change from baseline in FBG at 12 months n=59 Baseline FPG: 183.8 mg/dL FPG at 12 mos: 126.1 mg/dL Mean change: -3.0% (95% CI NR; p<0.001)	NA NA NA	SAEs 19 (29%) TEAEs: 59 (89.4%) Death: 3 (4.5%) p-values and CI not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Open-label, single arm study. No randomization performed. Performance Bias: High. No blinding of patients, caregivers, or investigators. Detection Bias: High. No comparator was used to evaluate therapy. Attrition Bias: High. Significant attrition due to nonadherence, lack of efficacy, transfer to another study, and death. Reporting Bias: High. LOCF used for missing data ≥ 6 mos post baseline. Patients with no observational data before 6 mos were excluded from final analysis, therefore mITT population was analyzed. Other Bias: Unclear. Study funded by NIH. Manufacturer provided funding for medical writing of manuscript. Several authors report serving as consultants and/or receiving funding from the manufacturer. **Applicability**: Patient: Small study population due to the nature of the rare condition. Population was mostly female, which reflects the prevalence of the condition. Intervention: Metreleptin dosing studied in Phase 2 phase of the open-label extension study. FDA has approved dosing used in this study. Comparator: Single-arm study design, no comparator was used.

		--Diabetic or fasting insulin > 30 micro units/mL and/or --Fasting TG > 200 mg/dL or non-fasting TG > 500 mg/dL Key Exclusion Criteria: -HIV -Infectious liver disease -Taking weight loss drugs						Outcomes: Surrogate outcomes included changes in HbA1C and fasting TG levels from baseline to 12 mos. Metabolic changes are the clinically accepted metrics used to evaluate complications of leptin deficiency. Setting: Single site at the NIH in Bethesda, Maryland with patients originating from the United States, European Union, South America, Canada, India, Pakistan, and Saudi Arabia
Abbreviations: CI = confidence interval; dL = deciliters; DM = diabetes mellitus; FDA = Food and Drug Administration; FPG = fasting blood glucose; GL = generalized lipodystrophy; HbA1c = hemoglobin A1C; HIV = human immunodeficiency virus; ITT = intention to treat; kg = kilograms; LOCF = last observation carried forward; LD = lipodystrophy; mg = milligrams; mITT = modified intention to treat; mL = milliliters; mmol = millimoles; mos = months; N = number of subjects; NA = not applicable; ng = nanograms; NIH = National Institutes of Health; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; SAEs = serious adverse events; SC = subcutaneous; TEAEs = treatment-emergent adverse events; TG = triglycerides; yo = years old; yrs = years								

References:

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8. Metreleptin (Myalepta): Therapeutic area: Leptin deficiency in lipodystrophy: Reimbursement Review . Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2024 Oct. Report No.: SR0784-Clinical Review. PMID: 39652691. https://www.cda-amc.ca/sites/default/files/DRR/2024/SR0784REC-Myalepta.pdf Accessed January 16, 2026.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MYALEPT® (metreleptin) for injection, for subcutaneous use
Initial U.S. Approval: 2014

WARNING: RISK OF ANTI-METRELEPTIN ANTIBODIES WITH NEUTRALIZING ACTIVITY AND RISK OF LYMPHOMA

See full prescribing information for complete boxed warning.

Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with MYALEPT. The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of MYALEPT efficacy. Worsening metabolic control and/or severe infection have been reported. Test for anti-metreleptin antibodies with neutralizing activity in patients with severe infections or loss of efficacy during MYALEPT treatment. Contact Chiesi Farmaceutici S.p.A. at 1-866-216-1526 for neutralizing antibody testing. (4.1, 5.1)

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with MYALEPT. Carefully consider the benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. (5.2)

MYALEPT is available only through a restricted program called the MYALEPT REMS PROGRAM. (5.3)

INDICATIONS AND USAGE

MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. (1)

Limitations of Use

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established. (1)
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established. (1)
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy. (1)
- MYALEPT is not indicated for use in patients with metabolic disease, without concurrent evidence of generalized lipodystrophy. (1)

DOSAGE AND ADMINISTRATION

Administer as a subcutaneous injection once daily after the lyophilized cake is reconstituted with Bacteriostatic Water for Injection (BWFI) or preservative-free sterile Water for Injection (WFI). (2.1)

The recommended daily dosages are:

- Body weight 40 kg or less: starting dose 0.06 mg/kg/day, increase or decrease by 0.02 mg/kg to a maximum daily dose of 0.13 mg/kg. (2.1)
- Males greater than 40 kg body weight: starting dose 2.5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day to a maximum dose of 10 mg/day. (2.1)
- Females greater than 40 kg body weight: starting dose 5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day to a maximum dose of 10 mg/day. (2.1)

DOSAGE FORMS AND STRENGTHS

MYALEPT is supplied as a sterile, white, solid, lyophilized cake of 11.3 mg metreleptin per vial to deliver 5 mg per mL when reconstituted in 2.2 mL of BWFI or WFI. (3)

CONTRAINDICATIONS

- General obesity not associated with congenital leptin deficiency. (4.1)
- Hypersensitivity to metreleptin. (4.2)

WARNINGS AND PRECAUTIONS

- Anti-metreleptin antibodies with neutralizing activity: Could inhibit endogenous leptin action and/or result in loss of MYALEPT efficacy. Test for neutralizing antibodies in patients with severe infections or loss of efficacy during MYALEPT treatment. (5.1)
- T-cell lymphoma: Carefully consider benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. (5.2)
- Hypoglycemia: A dose adjustment, including possible large reductions, of insulin or insulin secretagogue may be necessary. Closely monitor blood glucose in patients on concomitant insulin or insulin secretagogue therapy. (5.4)
- Autoimmunity: Autoimmune disorder progression has been observed in patients treated with MYALEPT. Carefully consider benefits and risks of MYALEPT treatment in patients with autoimmune disease. (5.5)
- Hypersensitivity: Hypersensitivity reactions (e.g., anaphylaxis, urticaria or generalized rash) have been reported. Patient should promptly seek medical advice regarding suspected reactions. (5.6)
- Benzyl Alcohol Toxicity: Preservative-free sterile WFI recommended for neonates and infants. (5.7)

ADVERSE REACTIONS

Most common in clinical trials (≥10%): headache, hypoglycemia, decreased weight, abdominal pain. (5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi Farmaceutici S.p.A. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2024

Metreleptin (MYALEPT®)

Goal(s):

- Promote evidence-based standard of care in patients diagnosed with lipodystrophy due to leptin deficiency.
- Limit to populations in which metreleptin has been studied and approved by the Food and Drug Administration.

Length of Authorization:

- Up to 12 months

Requires PA:

- Metreleptin (pharmacy and physician administered claims)

Covered Populations: FFS patients

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 a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved age and indication?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Does the patient have any of the following diagnoses: • Partial lipodystrophy • Non-alcoholic steatohepatitis (NASH) or metabolic dysfunction-associated steatohepatitis (MASH) • General obesity not associated with congenital leptin deficiency • HIV-related lipodystrophy or • Metabolic disease (diabetes, hypertriglyceridemia) without evidence of generalized lipodystrophy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Is the drug prescribed by an endocrinologist or a provider with experience in managing lipodystrophy due to leptin deficiency?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Are there documented baseline assessments for all of the following within the past year: • Serum leptin level • Hemoglobin A1C • Fasting triglycerides	**Yes**: Go to #7 Document date and lab results_____	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have: • Persistent hyperglycemia (HbA1c > 6.5%) despite dietary interventions AND • Persistent fasting hypertriglyceridemia (TG > 200 mg/dL) despite dietary interventions	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient on maximally tolerated therapy for diagnosed diabetes and hypertriglyceridemia when applicable with the following medications: • Optimized diabetes therapy (insulin, metformin, GLP-1 antagonist, or SGLT-2 inhibitor) at maximum tolerated dose for at least 6 months • Optimized therapy with at least 2 triglyceride-lowering agents (e.g., fibrates, statins) at maximum tolerated doses for at least 6 months • Or do they have documented age or co-morbidity contraindication to these medications	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence of adherence and tolerance to therapy based on claims history and provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the provider re-evaluated the following baseline assessments based upon pre-existing diagnoses within the past 6 months? • HbA1c • Serum triglycerides	**Yes:** Go to #3 Document date and lab values_____	**No:** Pass to RPh. Deny; medical appropriateness
3. Has A1C reduced by at least 0.5% from baseline or have fasting triglycerides reduced by at 15%?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/26 (DM)
Implementation: TBD

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Drug Class Literature Scan: Cephalosporins

Date of Review: April 2026

Date of Last Review: January 2015
Literature Search: 10/01/14 – 01/21/26

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

Plain Language Summary:

- Cephalosporins are medicines used to treat different types of infections caused by germs, also known as bacteria. They are commonly used for the treatment of skin infections and lung infections, like pneumonia.
- Guidelines published since the last review recommend cephalosporins as an initial treatment for Lyme disease rash (erythema migrans), pneumonia, infections that are spread by sexual contact, and foot infections in people that have diabetes.
- Evidence also recommends cephalosporins to treat infections after other antibiotics have been tried or in special circumstances, for example when someone has an antibiotic allergy or is pregnant. Examples of these types of conditions are urinary tract infections, ear infections, and skin infections.
- Providers are asked to prescribe a cephalosporin that is on the preferred drug list if it is a good choice for the patient. If a provider prescribes a non-preferred cephalosporin, they must explain to the Oregon Health Authority why the patient needs that medicine before Oregon Health Plan will pay for it. This is called prior authorization. The Drug Use Research and Management (DURM) group recommends making cefuroxime, cefaclor, and cefpodoxime preferred to increase access to therapies that are recommended by guidelines.

Conclusions:

- Cephalosporins are effective against gram negative, gram positive, and aerobic bacteria.[1] Oral cephalosporins are classified as first generation (i.e., cefadroxil, cephalexin, and cephradine), second generation (i.e., cefaclor, cefprozil, cefuroxime, and loracarbef) and third generation (i.e., cefdinir, cefixime, and cefpodoxime).[1] First generation cephalosporins are active against most gram-positive infections except for methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*. First generation agents are effective against *Escherichia coli, Proteus mirabilis, and Klebsiella pneumoniae*. Second generation cephalosporins have activity against *Haemophilus influenzae, Moraxella catarrhalis* and *Bacteroides*.[1] The third generation cephalosporins have less activity against gram-positive bacteria but are effective in treating Enterobacterales, *Neisseria sp.,* and *H. influenzae*. Ceftazidime, a third-generation cephalosporin, also has efficacy against *Pseudomonas aeruginosa*.
- Antimicrobial susceptibility data from 2024 and 2025 supplied by Oregon hospitals reported on 2 oral cephalosporins. Testing of samples shows cefazolin has high efficacy (85% or higher) against the following bacteria: *E. coli, K. pneumoniae*, *P. mirabilis*, *Staphylococcus aureus, Staphylococcus lugdunensis*, and *Streptococcus agalactiae* (Group B). Cefazolin has not shown to be effective against multi-drug resistant forms of the above bacteria. Cefpodoxime was effective for similar gram-negative bacteria as cefazolin and also had activity against *Enterobacter cloacae* complex and *Klebsiella oxytoca*. Susceptibility reporting on other oral cephalosporins was not provided.

Author: Kathy Sentena, PharmD

- This review identified 12 new guidelines for inclusion. Oral cephalosporins are recommended as first line treatment options for erythema migrans associated Lyme Disease (i.e., cefuroxime), severe cellulitis infections (i.e., cefuroxime), recurrent cystitis in pregnant women (i.e., cephalexin or cefaclor), community acquired pneumonia (CAP) in patients with risk factors (i.e., cefpodoxime or cefuroxime in combination with other antibiotics), mild diabetic foot infections (DFI) (i.e., cephalexin) and moderate to severe DFIs (i.e., cefuroxime).
- Guidance by the Infectious Disease Society of American (IDSA) for complicated urinary tract infections (cUTI) recommend the use of intravenous (IV) cephalosporins for patients with sepsis and oral therapy as a second line option in patients without sepsis.[2]
- A 2020 American Academy of Neurology (AAN)/American College of Rheumatology (ACR)/IDSA guideline recommends the use of oral cefuroxime for erythema migrans (circular skin rash) and IV cefuroxime for patients with neurological symptoms of Lyme disease or Lyme carditis.[3]
- Cephalexin is recommended by the National Institute for Health and Care Excellence (NICE) as a second-line treatment option for recurrent urinary tract infections (UTIs).[4]
- The NICE guidelines recommend the use of ceftriaxone for most cases of bacterial meningitis and meningococcal disease as empiric therapy and when susceptible causative organisms are identified.[5]
- When antibiotics are indicated, NICE recommends treatment of acute otitis media with amoxicillin first-line; however, there is no evidence of major treatment differences demonstrated between the penicillins, cephalosporins and macrolides.[6]
- For the treatment of cellulitis NICE recommends cefuroxime and ceftriaxone as options if infections are considered severe.[7]
- Guidance by NICE in a 2019 recommendation on the treatment of diverticulitis in adult patients recommends cephalexin with metronidazole as an alternative option to amoxicillin/clavulanate, if clinically indicated.[8] Most people with acute diverticulitis do not require antibiotic treatment.
- If IV therapy is indicated, cephalosporins are recommended by NICE for the prophylaxis and treatment of human and animal bites.[9]
- The European Association of Urology (EAU) 2025 guidelines recommend the use of cephalosporin in certain circumstances based on infecting organism, location, resistance patterns and adverse events.[10]
- The cephalosporins, cefuroxime and cefpodoxime, are recommended by the American Thoracic Society (ATS) and IDSA 2019 guidelines for the outpatient treatment of CAP for patients that have risk factors, such as diabetes or cancer.[11]
- First generation cephalosporins are recommended by the International Working Group on the Diabetic Foot (IWGDF)/IDSA 2023 for the treatment of mild DFI in patients that have no complicating features. For moderate to severe infections, second or third generation cephalosporins are recommended.[12]
- The Centers for Disease Control and Prevention (CDC) published guidelines for the treatment of sexually transmitted diseases (STD) in 2021.[13] The use of ceftriaxone intramuscular (IM) or IV is routinely recommended for the treatment of different types of Neisseria gonorrhoeae infections.[13]

Recommendations:
- Consider making cefuroxime, cefaclor and cefpodoxime preferred based on guideline recommendations.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- A previous review of the cephalosporins in 2015 by the DURM group found no difference in efficacy or safety between the cephalosporins within the same generation.
- A recommendation was implemented to offer at least one oral medication from each of the first, second and third generation cephalosporin classes to be preferred in addition to cefuroxime oral suspension due to cost effectiveness.

- Cephalexin capsules and suspension, cefprozil tablets and suspension, cefuroxime capsules and cefdinir capsules and suspension are preferred (see Appendix 1).
- Non-preferred products are subject to the general non-preferred drug prior authorization (PA) criteria.

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. Medline search strategy used for this literature scan 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), NICE, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:
After review, 4 systematic reviews were excluded due to poor quality, 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]

New Guidelines:
High Quality Guidelines:

<u>IDSA – Management and Treatment of Complicated Urinary Tract Infections</u>
A 2025 guidance from the IDSA updated previous recommendation for the treatment of cUTI.[2] The literature was searched from 2008 -2023. Older studies were excluded due to changing resistance patterns, in which results may not be applicable to current trends. Resistance rates were required to be reported to be included in the analysis. Recommendations for patients with sepsis, without sepsis and oral therapy will be presented.

For the empiric antibiotic treatment of cUTI, IDSA recommends specific treatment based on presence or absence of sepsis.[2] Outpatient management with oral therapy may be appropriate for some patients with pyelonephritis. Empiric therapy options are outlined in **Table 1**. Certain oral first or second generation-cephalosporins are recommended as alternative options in select settings for patient with cUTI without sepsis; however, they are less well studied and no specific therapy was recommended. Due to high resistance rates to fluoroquinolones and trimethoprim (TMP)/sulfamethoxazole (SMX), prior urine cultures are helpful if available.[2] In patients with cUTI and gram-negative infections, observational data has demonstrated that third-generation oral cephalosporins may have similar efficacy to fluoroquinolones or TMP-SMX. In patients with sepsis, antibiograms can be helpful to determine empiric therapy if it is local, recent and relevant to the patient (conditional recommendation; low quality of evidence).[2] Nitrofurantoin and oral fosfomycin are generally not recommended for cUTI because they may not achieve adequate levels in renal parenchyma and blood.

Table 1. IDSA Guidance for the Empiric Treatment of Complicated Urinary Tract Infection[2]

Indication	Preferred	Alternative	Strength of Recommendation

Sepsis with or without shock	Third- or fourth-generation cephalosporins (i.e., IV ceftriaxone, IV ceftazidime, IV cefotaxime and IV cefepime), carbapenems*, piperacillin-tazobactam, fluoroquinolones^	Novel beta lactam-beta lactamase inhibitors±; cefiderocol, plazomicin or older aminoglycosides+	Conditional recommendation; very low to moderate quality evidence. Moderate evidence for all classes except cephalosporins and older aminoglycosides which had very low quality of evidence.
Without sepsis, IV route of therapy	Third- or fourth-generation cephalosporins (i.e., IV ceftriaxone, IV ceftazidime, IV cefotaxime and IV cefepime), piperacillin-tazobactam, fluoroquinolones^	Carbapenems*, newer agents (novel beta lactams-beta lactamase inhibitors, cefiderocol, plazomicin), or older aminoglycosides+.	Conditional recommendation; very low to moderate quality evidence. Moderate evidence for all classes except cephalosporins and older aminoglycosides which had very low quality of evidence.
Without sepsis, oral route of therapy	Fluoroquinolones^ or trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate or oral cephalosporins (i.e., cefixime, cefpodoxime, cefuroxime, cephalexin)	Conditional recommendation; very low to moderate quality evidence. Moderate evidence for all classes except cephalosporins and older aminoglycosides which had very low quality of evidence.
Key: * Carbapenems recommended are imipenem-cilastatin, doripenem, meropenem and ertapenem; ^ Approved fluoroquinolones for UTI are ciprofloxacin and levofloxacin; + The older aminoglycosides recommended are gentamicin, amikacin, and tobramycin; ± Include ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam. Abbreviations: IV – intravenous; UTI – urinary tract infection.			

AAN/ACR/IDSA – 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease

A multidisciplinary panel developed guidelines for managing Lyme disease. Methodology for the development of IDSA guidelines was followed to develop recommendations.[3] Antibiotic prophylaxis with a single doxycycline dose (200 mg for adults and 4.4 mg/kg for children up to 200 mg) is recommended for high-risk tick bites based on moderate-quality evidence (strong recommendation).[3] For those individuals with erythema migrans oral doxycycline (10 days), amoxicillin (14 days), or cefuroxime (14 days) is recommended (strong recommendation, moderate-quality of evidence).[3] Azithromycin 5-10 days can be used as a second-line agent.[3] In patients with neurological symptoms of Lyme disease without brain or spinal cord involvement, the recommendation is to treat the patient with IV ceftriaxone, cefotaxime, penicillin G, or oral doxycycline for a total of 14-21 days (strong recommendation, moderate-quality of evidence).[3] For patients with brain or spinal cord involvement related to Lyme disease, IV antibiotics are recommended over oral antibiotics (strong recommendation, moderate-quality of evidence). For the treatment of Lyme carditis 14-21 days of IV ceftriaxone is recommended, switching to an oral option (i.e., doxycycline, amoxicillin, cefuroxime, or azithromycin) when patient demonstrates clinical improvement (weak recommendation, very low-quality evidence).[3] If an initial course of oral antibiotics, in which a specific antibiotic was not recommended, is not effective at reducing Lyme arthritis, a 2–4-week course of IV ceftriaxone is recommended (weak recommendation, low-quality evidence).[3]

NICE – Recurrent Urinary Tract Infection: Antimicrobial Prescribing

The NICE updated guidance on the treatment of recurrent UTIs in 2024.[4] Behavioral and personal hygiene measures are recommended before routine antibiotic use. Underlying causes should also be ruled out.

If antibiotics are indicated, local antimicrobial resistance patterns should be considered. For patients who are 16 years and older, antiseptic prophylaxis with off-label methenamine hippurate, 1 g twice daily, may be used.[4] Recommended first-line antibiotic therapy includes: trimethoprim 200 mg single dose when exposed to trigger, or 100 mg at nightly, or nitrofurantoin 100 mg as a single dose when exposed to trigger, or 50 mg to 100 mg each night.[4] Second-line options include amoxicillin 500 mg single dose when exposed to trigger or 125 mg nightly or cephalexin 500 mg as a single dose when exposed to trigger or 125 mg each night.[4] For those 16 years of age and younger, but older than 3 months, first choice antibiotics are trimethoprim and nitrofurantoin (see guidance for dosing).[4] Second-line treatments include amoxicillin (see guidance for dosing) and cephalexin 12.5 mg/kg at night with a maximum of 125 mg per dose.[4] Children under 3 months should be referred to a specialist. Treatment should be reassessed at least every 6 months.

NICE – Bacterial Meningitis and Meningococcal Disease

In March of 2024 NICE published recommendations for recognizing, diagnosing and managing bacterial meningitis and meningococcal disease.[5] The recommended treatment options will be covered in this review.

Intravenous ceftriaxone is recommended as empiric therapy for bacterial meningitis in the hospital. Cefotaxime, given IV, is recommended if ceftriaxone is contraindicated. Intravenous amoxicillin is recommended to be given with ceftriaxone or cefotaxime if the patient has risk factors for Listeria monocytogenes.[5] Antibiotics should be continued until testing suggests an alternative treatment is indicated. Ceftriaxone, or cefotaxime as an alternative, is recommended if it is known that *S. pneumoniae* is the causative organism.[5] Therapy for 10 days is recommended if the patient has recovered and if they have not recovered then an infection specialist should be consulted. If the causative organism is *H. influenzae* type b, ceftriaxone or alternatively cefotaxime if ceftriaxone is contraindicated, is recommended 7 days or up to 10 days if indicated.[5] Ceftriaxone, or cefotaxime if ceftriaxone is contraindicated, is recommended for 14 days for Group B *S Streptococcus* and an infection specialist consult is recommended.[5] If the meningitis is caused by *Enterobacterales*, ceftriaxone, or cefotaxime if ceftriaxone is contraindicated, is recommended for 21 days and an infection specialist should be consulted. *Neisseria meningitis* should be treated with 5 days of ceftriaxone, or cefotaxime if ceftriaxone is contraindicated.[5]

Intravenous ceftriaxone is recommended or confirmed meningococcal disease in the hospital. It should be given for 5 days if the patient has recovered, seek advice from an infection specialist if they have not recovered.[5]

NICE – Otitis Media Prescribing

National Institute for Health and Care Excellence updated guidance in March of 2022 for the use of antibiotics for otitis media.[6] Generally, most children and young people will not require antibiotics, as it has been shown that antibiotics have a small effect on symptom reduction. A back-up antibiotic prescription, only if needed, is recommended. Children under 2 years of age and those any age with otorrhea may be more likely to benefit from antibiotics.[6]

If antibiotics are prescribed, NICE found no differences between successful treatment rates of uncomplicated acute otitis media between the different classes of antibiotics (i.e., penicillins, cephalosporins, and macrolides), based on low- to moderate-quality evidence.[6] There is very low- to moderate-quality evidence that amoxicillin-clavulanate had significantly more adverse reactions compared to cephalosporins or azithromycin. Choice should be based on efforts to minimize resistance, such as choosing a narrow-spectrum antibiotic.[6] In general, amoxicillin (125 mg to 500 mg three times a day) should be offered first-line.

Clarithromycin is an alternative first-line option. Amoxicillin-clavulanate is recommended as an appropriate second-line choice if symptoms worsen after first-choice antibiotic is administered for 2-3 days.[6] Five to seven days of antibiotic is recommended.[6]

NICE – Cellulitis and Erysipelas

Recommendations for the use of antibiotics in adults and children were updated in 2019 by NICE.[7] Antibiotic recommendations in adults 18 years and older are for flucloxacillin as first-line, which is not available in the US. Other first-line options are clarithromycin, erythromycin, and doxycycline. If the infection is near the eyes or nose then amoxicillin-clavulanate is recommended first-line or clarithromycin with metronidazole if amoxicillin-clavulanate is not an option.[7] For severe infections amoxicillin-clavulanate, cefuroxime, ceftriaxone or clindamycin is recommended. If MRSA is suspected or confirmed then a specialist may be consulted for specific combination therapies from previously mentioned therapies. Vancomycin and linezolid may also be considered.[7] If the patient is pregnant, erythromycin is the preferred macrolide. Oral therapy should be used if infection severity does not require IV antibiotics. Up to 14 days of therapy may be required for full resolution of symptoms.

For children 1 month or older amoxicillin-clavulanate, clarithromycin, and erythromycin is recommended.[7] If the infection is near the eyes and nose amoxicillin-clavulanate is recommended first-line. Alternative options are clarithromycin with metronidazole, cefuroxime, and clindamycin. Vancomycin and linezolid are recommended for MRSA.[7]

NICE – Human and Animal Bite Treatment Recommendations

In 2020 NICE guidelines published treatment recommendations for adults and children with human or animal bites.[9] For patients 18 years and older give antibiotics for prophylaxis for 3 days and treatment for 5 days, with longer duration of therapy if clinically indicated. First-line treatment is amoxicillin/clavulanate 250/125 mg or 500/125 mg three times a day.[9] Alternative options are doxycycline 200 mg on the first day, then 100 mg or 200 mg daily with metronidazole 400 mg three times daily.[9] If IV antibiotics are indicated the first-choice is amoxicillin/clavulanate 1.2 grams three times day.[9] Alternative choices are cefuroxime 750 mg three times daily with metronidazole 500 mg three times daily or ceftriaxone 2 g daily with metronidazole 500 mg three times daily.[9] A specialist should be consulted for children less than one month. For children 1 month and older weight-based dosing of amoxicillin/clavulanate is recommended as the first-line treatment option. Alternative regimens are trimethoprim/sulfamethoxazole for children under 1 year and doxycycline with metronidazole for children 12-17 years.[9] Amoxicillin/clavulanate, cefuroxime with metronidazole, or ceftriaxone with metronidazole are recommended.[9]

NICE – Diverticular Disease

Guidance on the management and treatment of diverticulitis was published by NICE in 2019.[8] Antibiotics are not routinely recommended for treatment of this condition; however, antibiotics may be offered for patients with acute diverticulitis if they are systemically unwell, immunocompromised or they have significant comorbidities such as diabetes or uncontrolled hypertension. Intravenous antibiotics should be used for people with complicated acute diverticulitis that are admitted to the hospital.[8]

For adults, 18 years and older, amoxicillin/clavulanate is recommended first line for uncomplicated acute diverticulitis.[8] Five days of cephalexin with metronidazole and trimethoprim with metronidazole are recommended as alternative choices for acute diverticulitis. If the patient is diagnosed with complicated acute diverticulitis, recommendations include: IV amoxicillin/clavulanate, cefuroxime plus metronidazole, amoxicillin plus gentamicin and metronidazole, or ciprofloxacin plus metronidazole.[8] Up to 14 days of treatment may be needed for complicated infections and patients should be switched to oral therapy as soon as clinically appropriate.[8]

EAU – Urological Infections 2025

The EAU 2025 Guidelines provide updated recommendations for the use of antibiotics for urological infections.[10] Recommendations pertaining to antibiotic use will be presented. Evidence is graded from 1a (Highest Quality of Evidence) to 4 (Expert Opinion). Antibiotic selection should be guided by spectrum and susceptibility patterns, efficacy, tolerability, adverse reactions, costs and availability. Strength of recommendations range from Strong to Weak and are presented in **Table 2**. Cystitis is considered localized (i.e., no systemic infection in either sex) or systemic (i.e., pyelonephritis, prostatitis, etc.). Oral cephalosporins are not recommended for empiric therapy for cystitis due to risk of adverse effects on the environment (i.e., creating highly resistant organisms) and aminopenicillins are not recommended due to high resistance rates and increased selection for Extended-Spectrum Beta-Lactamase (ESBL)-producing bacteria, but both can be used in select cases (Strong recommendation).[10] Fluoroquinolones should not be used unless it is considered inappropriate to use other antibiotics.

Table 2. EAU Antibiotic Recommendations for People with Urological Infections[10]

Diagnosis	Antibiotic Recommendation	Comments / Strength of Recommendation
Cystitis	Pivmecillinam 400 mg three times daily for 3-5 days	• First-line option in women / Strong
	Fosfomycin trometamol 3 g as a single dose	• First-line option in women / Strong
	Nitrofurantoin monohydrate/macrocrystal or nitrofurantoin macrocrystal prolonged release 100 mg twice daily for 5 days	• First-line option in women / Strong
	TMP/SMX 160/800 mg twice daily for 3 days or trimethoprim alone 200 mg twice daily for 5 days	• Alternative option • First choice only in areas with known resistance rates for *E.coli* of <20%
	Cephalosporins (e.g. cefadroxil 500 mg twice daily for 3 days)	• Other comparable cephalosporins can be used
	TMP/SMX or fluoroquinolone for at least 7 days	• First-line in men due to risk of prostate involvement
Cystitis in Pregnancy	Penicillins, cephalosporins, fosfomycin, nitrofurantoin, trimethoprim and sulphonamides can be considered	• Check for patient allergies • Trimethoprim should not be used in the first trimester of pregnancy and TMP/SMX is not recommended in the last trimester of pregnancy
Prevention of Recurrent Cystitis	Nitrofurantoin 50 mg or 100 mg once daily Fosfomycin trometamol 3 g once a week Trimethoprim 100 mg once daily	• No evidence of statistically significant difference in efficacy between antibiotics for recurrent cystitis
	Cephalexin 125 or 250 mg once daily Cefaclor 250 mg once daily	• Recommended for pregnant women with cystitis
Pyelonephritis (outpatient)	Fluoroquinolones (i.e., ciprofloxacin, levofloxacin) Cephalosporins (i.e., cefpodoxime, ceftibuten) TMP/SMX	• Fluoroquinolones are first-line / Strong • Only classes recommended for oral empirical therapy • If any class is used besides a fluoroquinolone, an initial intravenous dose of long-acting parenteral antimicrobial (e.g., ceftriaxone) should be used
Urethritis	Ceftriaxone and azithromycin for genitourinary urethritis	• Recommended first-line / Level 2a

		• Use nucleic acid amplification test (NAAT) to guide treatment
	Ceftriaxone 1-2 gm intramuscular or intravenously as a single dose Doxycycline 100 mg twice daily for 7 days	• For gonococcal infections
	Doxycycline 100 mg twice daily for 7 days	• For non-gonococcal infections (e.g., *Chlamydia trachomatis*)
	Azithromycin 1 gm day one and 500 mg days 2-4	• For *Mycoplasma genitalium*
	Doxycycline 100 mg twice daily for 7 days	• For *Ureaplasma urealyticum*
	Metronidazole 1.5-2 gm as a single dose	• For *Trichomonas vaginalis*
Acute Bacterial Prostatitis	Fluoroquinolone for 4-6 weeks	• First-line for empirical treatment
	Doxycycline 100 mg twice daily for 10 days	• Only for *C. trachomatis* or mycoplasma infections
	Azithromycin 500 mg once daily for up to 3 weeks	• Only for *C. trachomatis*
	Metronidazole 500 mg three times daily for 14 days	• Only for *T. vaginalis*
Chronic Bacterial Prostatitis	Fluoroquinolone	• First-line / Strong
	Doxycycline	• Only for *C. trachomatis*
	Macrolide	• If intra-cellular bacteria / Strong
	Metronidazole	• For *Trichomonas vaginalis* / Strong
Abbreviation: TMP/SMX – trimethoprim/sulfamethoxazole		

ATS – Treatment of Community-acquired Pneumonia

Guidelines for the diagnosis and treatment of adults with CAP were published in 2019 by the ATS and IDSA.[11] Treatment of CAP in the outpatient setting will be presented. Initial treatment strategies for patients with CAP are based on the presence or absence of additional risk factors **(Table 3)**.[11] There is no evidence demonstrating specific antibiotic regimens being superior or equivalent for the treatment of CAP. Duration of antibiotic therapy should be based on the clinical response of the patient but for no less than 5 days of treatment (strong recommendation, moderate quality of evidence).[11]

Table 3. Outpatient Initial Treatment of Community Acquired Pneumonia[11]

Patient Characteristics	Antibiotic Recommendation	Strength of Recommendation
If the patient has no comorbidities or risk factors for *methicillin-resistant Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*	• amoxicillin 1 gm 3 times a day	Strong recommendation, moderate quality of evidence
	• doxycycline 100 mg 2 times	Conditional recommendation, low quality of evidence
	• azithromycin 500 mg on day 1 and then 250 mg daily OR • clarithromycin 500 mg 2 times daily OR • clarithromycin ER 1,000 mg daily	Conditional recommendation, moderate quality of evidence - Only use macrolide if local pneumococcal resistance is <25%

If the patient has risk factors, such as chronic heart, lung, liver, renal disease, diabetes, alcoholism, asplenia or malignancy	*Combination Therapy* <u>Amoxicillin/clavulanate + Macrolide</u> • amoxicillin/clavulanate (dosed at 500 mg/125 mg 3 times daily, 875 mg/125 mg twice daily, or 2000 mg/125 mg twice daily) PLUS • azithromycin 500 mg on day 1 and 250 mg daily <u>Amoxicillin/clavulanate + Clarithromycin</u> • amoxicillin/clavulanate (dosed at 500 mg/125 mg 3 times daily, 875 mg/125 mg twice daily, or 2000 mg/125 mg twice daily) PLUS • clarithromycin 500 mg twice daily or extended release 1,000 mg daily <u>Amoxicillin/clavulanate + Doxycycline</u> • amoxicillin/clavulanate (dosed at 500 mg/125 mg 3 times daily, 875 mg/125 mg twice daily, or 2000 mg/125 mg twice daily) PLUS • doxycycline 100 mg twice daily <u>Cephalosporin + Macrolide</u> • cefpodoxime 200 mg 2 times daily OR cefuroxime 500 mg 2 times daily PLUS • azithromycin 500 mg on day 1 and 250 mg daily <u>Cephalosporin + Clarithromycin</u> • cefpodoxime 200 mg 2 times daily OR cefuroxime 500 mg 2 times daily PLUS • clarithromycin 500 mg twice daily or extended release 1,000 mg daily OR	Strong recommendation, moderate quality of evidence (for all combinations except for those containing doxycycline) The recommendation for doxycycline is a conditional recommendation, low quality of evidence

	<u>Cephalosporin + Doxycycline</u> • cefpodoxime 200 mg 2 times daily OR cefuroxime 500 mg 2 times daily PLUS • doxycycline 100 mg twice daily	
	Monotherapy • levofloxacin 750 mg daily • moxifloxacin 400 mg daily	Strong recommendation, moderate quality of evidence

<u>IDSA – Diagnosis and Treatment of Diabetic Foot Infections</u>

The IWGDF and IDSA published a guideline in 2023 on managing foot infections in patients with diabetes.[12] Recommendations related to treating DFI with antibiotics will be presented. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) range from Strong (benefits clearly outweigh harm) or Weak/Conditional (benefits and risks are balanced) the certainty of evidence was designated from low to high.

<u>Recommendations Pertaining to Treatment are as follows:</u>

- Use systemic antibiotic regimens at standard dosing with evidence of efficacy to treat soft tissue infections in those with diabetes (Strong; High).[12]
- Antibiotics should be given for 1-2 weeks for DFI (Strong; High)[12]
- Antibiotic treatment duration of 3-4 weeks can be considered if the infection is improving, but extensive and slowly resolving or if the patient has peripheral arterial disease (PAD) (Conditional; Low).[12]
- The patient should receive additional diagnostic studies if the infection has not cleared after 4 weeks (Strong; Low).[12]
- Antibiotic selection should be based on the following (Best Practice Statement)[12]:
    - Likely or proven causative pathogen
    - Antibiotic susceptibility of the pathogen
    - Clinical severity of the infection
    - Evidence of efficacy of antibiotic for the treatment of DFI
    - Risk of adverse events, collateral damage of commensal flora, drug interactions, availability and cost.
- Only target gram-positive organisms (i.e., beta-hemolytic streptococci and *S. aureus*) in people with mild DFI who have not recently received antibiotic therapy and who reside in North America or Western Europe (Best Practice Statement).[12]
- Do not empirically target *P. aeruginosa* in temperate climates but use empirical treatment of *P. aeruginosa* if it has previously been isolated from the infection within the previous few weeks and the patient has a moderate to severe infection and live is Asia or North Africa (Best Practice Statement).[12]
- After minor amputation for diabetes related osteomyelitis of the foot and positive bone margin culture consider up to 3 weeks of antibiotics and up to 6 weeks for diabetes related foot osteomyelitis without bone resection or amputation (Conditional; Low).[12]

The most common causative pathogen of DFIs are gram-positive cocci (GPC) (i.e., staphylococci and streptococci).[12] Additional infecting organisms of concern are gram-negative rods (GNR) and strict anaerobes. For severe infections oral antibiotics are not recommended as initial therapy but may be considered for

follow-on therapy after initial parenteral therapy. Antibiotic selection should be based on clinical trial evidence and suspected pathogen. Evidence has demonstrated that no antibiotic class has be found to be superior to another for DFI.[12] First generation cephalosporins (i.e., cephalexin) are recommended for mild DFI along with semisynthetic penicillinase-resistant penicillin (i.e., cloxacillin). For moderate or severe infections, second and third generation cephalosporins, such as cefuroxime, cefotaxime, ceftriaxone and ceftazidime are recommended, in addition to beta-lactam-beta lactamase inhibitors, semisynthetic penicillinase-resistant penicillins, glycopeptides, aminoglycosides, and carbapenems.[12]

CDC – Sexually Transmitted Infections Treatment Guidelines

In 2021 the CDC updated 2015 guidance on treating persons with STIs or who were at risk for them.[13] Updated recommendations pertaining to antibiotic use for the treatment of *Neisseria gonorrhoeae* was the only addition that pertained to this review. The use of cephalosporins will be discussed for treatment of STIs in which they are indicated.[13] Ceftriaxone IM or IV is most the most commonly recommended therapy for all types of gonococcal infections, as described below.

For the treatment of uncomplicated gonococcal infections of the cervix, urethra, or rectum ceftriaxone 500 mg IM for adults and adolescents weighing <150 kg.[13] A single dose of gentamicin 240 mg IM with azithromycin 2 grams orally or cefixime 800 mg orally can be given if ceftriaxone is not available. Ceftriaxone 500 mg IM as a single dose should be given for adults and adolescents weighing <150 kg (those weighing >150 kg should receive a 1 gram dose) with uncomplicated gonococcal infection of the pharynx.[13] Pregnant women with *N. gonorrhoeae* infections should be treated with ceftriaxone 500 mg as a single IM dose. If ceftriaxone cannot be used then an infectious disease specialist or STI clinical expert should be consulted. Ceftriaxone 1 gram IM should also be used for gonococcal conjunctivitis. Alternative options include cefotaxime 1 gram IV every 8 hours.[13] For gonococcal- related arthritis and arthritis-dermatitis syndrome ceftriaxone 1 gram IM or IV every 12 hours should be used.[13] Pelvic inflammatory disease (PID) is often caused by *N. gonorrhoeae* and *C. trachomatis*. For PID parenteral ceftriaxone 1 gram every 24 hours plus doxycycline 100 mg orally or IV every 12 hours plus metronidazole 500 mg. Cefotetan with doxycycline or cefoxitin with doxycycline are alternative regimens.[13] For women with mild to moderate PID therapy with ceftriaxone 500 mg IM as a single dose with doxycycline and metronidazole can be considered. Alternative regimens include cefoxitin with probenecid, doxycycline or other parenteral third generation cephalosporins with doxycycline.

Neonates who are diagnosed with gonococcal ophthalmia neonatorum should receive ceftriaxone 25-50 mg/kg IV or IM as a single dose, but not more than 250 mg.[13] Those neonates infected with disseminated gonococcal infection should be treated with IV or IM ceftriaxone or cefotaxime for 7 days or 10-14 days if meningitis is documented. Neonates without signs of gonococcal infection that are born to mothers with untreated gonorrhea infections should receive ceftriaxone 20-50 mg/kg body weight IV or IM as a single dose, not to exceed 250 mg.[13] In children who weigh 45 kg or more should be treated with the adult regimen for uncomplicated gonococcal infections of the vulvovaginitis, cervicitis, urethritis, pharyngitis or proctitis. Children who weigh 45 kg or less should be given ceftriaxone 25-50 mg/kg IV or IM as a single dose and not to exceed 250 mg IM. For children 45 kg or less and are diagnosed with bacteremia or arthritis should be given ceftriaxone 50 mg/kg IM or IV as a single dose once daily for 7 days, with a maximum of 2 g daily dose.[13] For children weighing 45 kg or more the dose is ceftriaxone 1 gram IM or IV as a single dose daily for 7 days. For acute epididymitis, which is most likely caused by chlamydia or gonorrhea, ceftriaxone 500 mg IM as a single dose with doxycycline is recommended.

Ceftriaxone or levofloxacin are recommended for acute epididymitis caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex).[13] Acute proctitis should be managed with ceftriaxone 500 mg IM as single dose plus doxycycline. If a female adolescent or adult patient has been subject to sexual assault they should be given ceftriaxone 500 mg IM as a single dose plus doxycycline plus metronidazole. The same regimen, without the metronidazole, is recommended for adult male sexual assault victims.[13]

After review, two guidelines were excluded due to poor quality or lack of relevant guidance on topic.[18,19]

New Formulations:
None identified.

New FDA Safety Alerts:
None identified.

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Appendix 1: Current Preferred Drug List

First-generation

Generic	Brand	Form	PDL
cephalexin	CEPHALEXIN	CAPSULE	Y
cephalexin	CEPHALEXIN	SUSP RECON	Y

cefadroxil	CEFADROXIL	CAPSULE	N
cefadroxil	CEFADROXIL	SUSP RECON	N
cefadroxil	CEFADROXIL	TABLET	N
cephalexin	CEPHALEXIN	CAPSULE	N
cephalexin	CEPHALEXIN	TABLET	N

Second-generation

Generic	Brand	Form	PDL
cefprozil	CEFPROZIL	SUSP RECON	Y
cefprozil	CEFPROZIL	TABLET	Y
cefuroxime axetil	CEFUROXIME	TABLET	Y
cefaclor	CEFACLOR	CAPSULE	N
cefaclor	CEFACLOR	SUSP RECON	N
cefaclor	CEFACLOR ER	TAB ER 12H	N
loracarbef	LORABID	CAPSULE	N
loracarbef	LORABID	SUSP RECON	N

Third-generation

Generic	Brand	Form	PDL
cefdinir	CEFDINIR	CAPSULE	Y
cefdinir	CEFDINIR	SUSP RECON	Y
cefixime	CEFIXIME	CAPSULE	N
cefixime	CEFIXIME	SUSP RECON	N
cefpodoxime proxetil	CEFPODOXIME PROXETIL	SUSP RECON	N
cefpodoxime proxetil	CEFPODOXIME PROXETIL	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 86 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).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 14, 2026

Search Strategy:

#	Searches	Results
1	cephalexin.mp. or Cephalexin/	4202
2	Cefadroxil/ or cefadroxil.mp.	831
3	cefprozil.mp. or Cefprozil/	349
4	Cefuroxime/ or cefuroxime.mp.	5990
5	Cefaclor/ or cefaclor.mp.	1934
6	loracarbef.mp.	209
7	Cefdinir/ or cefdinir.mp.	562
8	Cefixime/ or cefixime.mp.	2493
9	cefpodoxime.mp. or Cefpodoxime/	1009
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	14666
11	limit 10 to (english language and humans)	7998
12	limit 11 to yr="2014 -Current"	2343
13	limit 12 to (clinical trial, phase iii or guideline or meta analysis or network meta-analysis or practice guideline or "systematic review")	86

Appendix 4: Key Inclusion Criteria

Population	Individuals with bacterial infections
Intervention	Cephalosporin antibiotics
Comparator	Antibiotic treatment other than cephalosporins
Outcomes	Infection cure rates
Setting	Outpatient

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Drug Class Update: Acne and Rosacea

Date of Review: April 2026

Date of Last Review: February 2021
Dates of Literature Search: 12/1/2020 – 01/14/2026

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

Purpose for Class Update:
The purpose of this update is to evaluate new comparative evidence for efficacy or harms of medications used to treat acne since the previous update. Acne conglobata, acne fulminans, and severe cystic acne are funded conditions under the Oregon Health Plan (OHP). Rosacea will be funded with the Health Evidence Review Commission (HERC) benefit plan update in 2027. Evidence for rosacea treatments is also included in this drug class update.

Plain Language Summary:
- Acne is common skin condition caused by clogging of skin pores which leads to pimples, whiteheads and blackheads. These outbreaks occur on the face, chest, upper back, shoulders, and neck. Hormonal changes, excessive stress, and certain medications may trigger or worsen acne. Depending on its severity, acne can cause emotional distress, depression, and scar the skin.
- Acne treatment is usually started with an over-the-counter cream, gel, or lotion (benzoyl peroxide, salicylic acid) applied to the skin. If 6 to 8 weeks of treatment is not effective, prescription products applied to the skin (retinoids), or oral prescription medicines (antibiotics, retinoids, hormonal therapy) can be added. Oral retinoids may have unwanted side effects such as depression or birth defects if taken while pregnant.
- Rosacea is another common skin condition that causes facial redness (flushing), spider veins, or rash usually on the nose and cheeks. It may also cause eye or eyelid swelling. The cause of rosacea is not known, but flare-ups can be caused by emotional stress, alcohol, spicy foods, hot drinks, strenuous exercise, or spending time outside in the sun and wind.
- Treatments for rosacea include creams and gels (metronidazole, azelaic acid) applied to the skin (topical), oral medicines (doxycycline, isotretinoin), or light-based therapies. Rosacea that affects the eye may be treated with lubricating eye drops. In severe cases, oral antibiotics may be used to relieve the eyelid swelling.
- Oregon Health Plan (OHP) will pay for acne treatments including topical adapalene, benzoyl peroxide, clindamycin, dapsone, erythromycin, tretinoin, sulfacetamide and oral isotretinoin. For all other acne treatments, the provider must explain to the Oregon Health Authority (OHA) why a patient needs that product before Medicaid will pay for it. This process is called prior authorization.
- The Drug Use Research and Management group recommends paying for certain topical agents (metronidazole, azelaic acid) that are Food and Drug Administration (FDA)-approved for people with rosacea. All other rosacea treatments will require prior authorization before OHP will pay for them.

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Research Questions:

1. What is the comparative efficacy and effectiveness of treatments for acne or rosacea?
2. What are the comparative harms of treatments for acne or rosacea?
3. Are there subpopulations of patients in which a particular treatment for acne or rosacea would be more effective or associated with less harm?

Conclusions:

- This drug class review is limited by the lack of high-quality evidence from systematic reviews and guidelines which evaluate the comparative efficacy and safety of treatments for acne and rosacea. Since the last Pharmacy and Therapeutics (P & T) Committee review, one Cochrane systematic review and 3 high-quality guidelines have been published to guide treatment of acne. For the management of rosacea, one Cochrane systematic review and 5 high-quality guidelines were identified.

Acne Treatments

- A 2024 Cochrane Review evaluated the evidence on the efficacy and safety of topical therapies used in the treatment of acne vulgaris.[1] No high-certainty evidence for the effects of any therapy was identified.[1] The low-quality data for topical benzoyl peroxide, adapalene and clindamycin did not show that one treatment was more effective than the other.[1]
- The National Institute for Health and Care Excellence (NICE) updated guidance for acne vulgaris management in 2023.[2] The current guidelines recommend topical benzoyl peroxide combined with topical clindamycin for mild to moderate acne, and combined topical adapalene and topical benzoyl peroxide or topical azelaic acid combined with oral doxycycline for moderate to severe acne.[2] In addition, for any severity of acne, either topical adapalene combined with topical benzoyl peroxide or topical retinoids combined with topical clindamycin may be used, but antibiotic monotherapy or topical therapy plus oral antibiotics are not recommended.[2]
- Canada's Drug Agency (CDA) does not recommend reimbursement of clascoterone cream due to insufficent comparative evidence with other acne treatments to assess the impact of clascoterone on improving skin clearance, reducing scarring, and improving quality of life (2025).[3] The CDA recommends that topical clindamycin/benzoyl peroxide/adapalene (CABTREO) gel be reimbursed by Canadian public drug plans for the topical treatment of acne vulgaris in patients 12 years of age and older only if pricing for this drug can be negotiated with participating plans so that the cost of treatment does not exceed other topical therapies (2024).[4]

Rosacea Treatments

- A 2015 Cochrane review assessed the efficacy and safety of treatments for rosacea.[5] High-quality evidence supports the effectiveness and safety of brimonidine topical gel in the management of erythema due to rosacea.[5] For management of papulopustular rosacea, topical metronidazole, azelaic acid, and ivermectin, or oral anti-inflammatory dose doxycycline monohydrate (40 mg), tetracycline and isotretinoin 0.3 mg/kg appear to be effective and safe for short-term use (moderate- to high-quality evidence).[5] There is no clear evidence that any one of the treatments for papulopustular rosacea, or any combination of treatments, has a particular advantage in terms of higher remission rates or fewer adverse effects.[5]
- In 2019 the American Acne and Rosacea Society (AARS) published rosacea management recommendations based upon available moderate-quality evidence and clinical experience.[6] Recommendations include:
    - Initial use of topical metronidazole or topical azelaic acid concurrently with oral doxycycline is recommended for treatment of severe papulopustular rosacea with transition to topical therapy alone after adequate response is achieved.[6]
    - Topical brimonidine and topical ivermectin are recommended for treatment of papulopustular rosacea with diffuse persistent facial erythema of at least moderate severity.[6]
    - For ocular rosacea, cyclosporin 0.05% ophthalmic emulsion was shown to be more beneficial than artificial tears (low-quality evidence).[6] Further studies on treatment of ocular rosacea are warranted.[6]

- Combination treatment with potassium titanyl phosphate laser and topical brimonidine is recommended for diffuse persistent facial erythema of rosacea.[6]

- The CDA has published 3 reviews for rosacea treatments. In 2015, the CDA recommended coverage of topical ivermectin for treatment of moderate to severe papulopustular rosacea if the drug plan cost for ivermectin did not exceed the drug plan cost of other topical rosacea treatments.[7] Due to insufficient evidence of comparative efficacy with doxycycline 100 mg, the CDA did not recommend coverage for oral doxycycline monohydrate 40 mg capsules (ORACEA) for treatment of rosacea (2013).[8] In 2011, the CDA recommended coverage of topical azelaic acid 15% gel for management of papulopustular rosacea.[9]
- In 2014, NICE reviewed the evidence for the use of topical brimonidine gel in management of facial erythema of rosacea.[10] NICE did not issue any recommendations for the use of brimonidine gel in rosacea but suggested that it may be an option for adults with moderate to severe rosacea and facial erythema. Specialists suggested that some people may only use brimonidine gel on days when they are particularly self-conscious about their appearance.[10] Before continuing long-term treatment with brimonidine gel, consideration should be given to how treatment efficacy can be assessed given the subjective nature of efficacy outcomes and the low response rates seen in clinical trials.[10]
- In 2016, NICE reviewed evidence for the use to topical ivermectin cream in treatment of inflammatory lesions associated with papulopustular rosacea.[11] NICE did not issue any recommendations for ivermectin cream in managing inflammatory lesions due to rosacea but suggested that mild to moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid and moderate or severe papulopustular rosacea is often managed with oral antibiotics (i.e., tetracycline, erythromycin, doxycycline).[11] At the time of the review, ivermectin cream was more costly than metronidazole or azelaic acid, so NICE recommended that local decision makers consider the available evidence on efficacy and safety as well as cost when making decisions about using ivermectin cream or another topical agent for papulopustular rosacea.[11]
- With the exception of oral isotretinoin, there is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for acne or rosacea.

New Formulations

- Two new formulations of topical agents were recently approved by the FDA for treatment of acne, and one oral product was approved for treatment of rosacea.
  - In July 2021, the FDA approved a new combination formulation of tretinoin 0.1% and benzoyl peroxide 3% (TWYNEO) cream indicated for topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older.[12]
  - In October 2023, the FDA approved a triple combination of clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1% (CABTREO) gel indicated for the topical treatment of acne vulgaris in adults and pediatric patients aged 12 years and older.[13]
  - A new oral formulation of minocycline 40 mg (EMROSI) received FDA approval in November 2024 and is indicated to treat inflammatory lesions of rosacea in adults.[14]

Recommendations:

- Make at least one generic topical metronidazole product approved for management of rosacea preferred. Make brimonidine nonpreferred based on clinical evidence. Created a new preferred drug list (PDL) class for rosacea treatments.
- Maintain TWYNEO and CABTREO as non-preferred medications on the PDL in rosacea topical medication class. Make EMROSI non-preferred on the PDL in the oral tetracycline drug class. No other changes to the PDL are recommended for acne and rosacea treatments.

- Revise acne prior authorization (PA) criteria to include non-preferred topical agents for management of rosacea and add documentation of baseline assessment of disease severity. Revise oral tetracycline PA criteria include baseline assessments of acne and rosacea, when prescribed for these indications. Add renewal criteria to topical acne/rosacea therapies and oral tetracyclines.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy:

- The acne drugs were last reviewed by the P &T Committee at the February 2021 meeting. Clascoterone topical cream was designated as non-preferred on the OHP PDL. No other changes were made to the PDL. The oral tetracyclines were last reviewed in March 2019. After review, 2 recently approved tetracyclines, omadacycline and sarecycline were maintained as non-preferred on the PDL. Sarecycline is no longer on the PDL as the drug is not eligible for federal rebates.
- Preferred acne treatments on the PDL include generic topical formulations of adapalene, benzoyl peroxide, clindamycin, dapsone, erythromycin, tretinoin, and sulfacetamide and oral isotretinoin. Single-source brand formulations are non-preferred on the PDL given lack of high-quality data to support their use in acne. Preferred oral tetracyclines include generic formulations of doxycycline suspension, tablets, and capsules and tetracycline tablets and capsules. PDL status for both classes of medications is presented in **Appendix 1**.
- Prior authorization (PA) criteria for the acne PDL class, includes federal legend topical medications that have FDA approval and an OHA-funded indication for severe acne vulgaris. Oral tetracyclines have a quantity limit to prevent inappropriate use beyond two, 14-day supplies in a 3-month time period. Use for all medications is limited to OHP-funded conditions (**Appendix 5**).
- Rosacea is not currently a funded indication on the HERC prioritized list.[15] However, with implementation of the benefit plan update in 2027, a pathway to coverage will be needed for rosacea treatments.

Background:

Acne

Acne vulgaris is a common skin condition, affecting more than 85% of adolescents and often continuing into adulthood.[16,17] Current research indicates that the pathogenesis of acne involves 4 main processes: follicular hyperproliferation, excess sebum production, inflammation, and proliferation of skin bacteria.[16,18] Various types of lesions can present in acne vulgaris: non-inflammatory lesions (blackheads and whiteheads) and inflammatory lesions including papules, pustules, cysts, and nodules that usually appear on the face, neck, upper back, and chest.[16] Acne, particularly severe acne, may result in permanent scarring and psychological morbidity such as poor self-esteem, depression, anxiety and suicidal ideation.[19] Acne vulgaris affects approximately 9% of the population worldwide (approximately 85% of individuals aged 12-24 years, and approximately 50% of patients aged 20-29 years).[19]

Acne vulgaris is classified based on patient age, lesion morphology (comedonal, inflammatory, mixed, nodulocystic), distribution (location on face, trunk, or both), and severity (extent, presence or absence of scarring, post inflammatory erythema, or hyperpigmentation).[19] Acne conglobata and acne fulminans are two forms of severe acne.[20] Acne conglobata is a severe form of nodular acne that involves recurrent abscesses and communicating sinuses and often results in disfiguring scars.[20] Acne fulminans is a severe variant of inflammatory acne that presents with severe ulceration and occasionally the systemic symptoms of fever and arthralgia.[20]

Numerous acne clinical grading and classification systems have been used in research and clinical settings to assess overall acne disease severity, lesion number and morphologies, affected anatomic sites, and associated secondary changes such as dyspigmentation and scarring.[21] Available grading systems include the

Investigator's Global Assessment (IGA), Leeds Revised Acne Grading System, Global Acne Grading System, Global Acne Severity Scale, and Comprehensive Acne Severity Scale.[21] While there is no universally accepted acne grading system in clinical settings, the IGA is most commonly used in the United States (US) and demonstrates good agreement between clinician and patient ratings.[21] The IGA scale has been used in many randomized controlled trials (RCTs) for acne treatments and is proposed as a cohesive framework upon which to establish an ideal acne grading system.[22] The IGA is a 5- or 6-point scale (0-5) that grades hyperpigmentation and erythema as clear, almost clear, mild, moderate, severe, and very severe.[23] A final IGA assessment of 0 to 1 (clear to almost clear) and at least a 2-grade improvement from baseline is defined by the Food and Drug Administration (FDA) as a clinically meaningful outcome for acne treatments.[23]

The main strategies for acne management are based on physiological targets: topical retinoids for comedolytic and keratolytic activity (minimizing comedonal plugging), antibiotics (doxycycline, minocycline) for antimicrobial and anti-inflammatory effects, hormonal therapies (contraceptives or spironolactone) targeting sebaceous gland activity, and systemic isotretinoin affecting all of these targets.[19] Topical therapies such as retinoids (e.g., tretinoin, adapalene), benzoyl peroxide, azelaic acid, and/or combinations of topical agents are first-line treatments for acne vulgaris.[19] Most topical preparations require at least 6 to 8 weeks before an improvement is seen, though response can be observed earlier with antibiotics (as early as 5 days) or later with retinoids (after 12 weeks).[3] For more severe disease, combinations of topical agents with systemic agents (oral antibiotics such as doxycycline and minocycline, hormonal therapies such as combination oral contraception or spironolactone, or isotretinoin) are recommended.[19] Isotretinoin is approved by the FDA for treating severe recalcitrant nodular acne but is often used to treat resistant or persistent moderate to severe acne, as well as acne that produces scarring or significant psychosocial distress.[19] These classes of medications are well-established and all have been FDA-approved for many years.

Rosacea

Rosacea is a chronic inflammatory skin disorder, primarily affecting the central face (cheeks, chin, nose and central forehead).[25] Rosacea often encompasses various combinations of symptoms including skin flushing, erythema, telangiectasias (fine, dilated blood vessels), edema, papules, pustules, ocular lesions and rhinophyma (bulbous nose) accompanied by itching, burning, or stinging.[26] Patients experience periods of exacerbation and remission, although facial redness is persistent.[27] Ocular involvement is found in more than 50% of rosacea patients, with symptoms including dryness, irritation, blepharitis, conjunctivitis and, more rarely, keratitis that may ultimately compromise eyesight.[27] Large retrospective database studies have yielded prevalence rates of rosacea ranging from 1.3% to 2.1%.[28] Rosacea occurs in both men and women, with similar prevalence rates.[29] Although it may occur at any age, the onset of rosacea typically begins at any time after age 30 years.[30] It has been most frequently observed in patients with fair skin but has also been diagnosed in Asians and African Americans.[26] In a survey on the racial/ethnic distribution of patients with rosacea, it was found that 2% of rosacea patients were Black, 2.3% were Asian or Pacific Islander, and 3.9% were Hispanic or Latino.[31] Rosacea can have a negative impact on quality of life, self-esteem, and well-being.[32]

In 2002, the National Rosacea Society outlined 4 distinct subtypes of rosacea.[30] The specific rosacea subtypes are presented in **Table 1**. With increasing knowledge of the pathophysiology of rosacea, a phenotype-based approach to diagnosis and management has evolved.[33] According to the 2019 Global Rosacea Consensus and National Rosacea Society there are 2 diagnostic phenotypes: 1) fixed centrofacial erythema with flushing, papules, pustules, and telangiectasia and 2) phymatous changes that may include ocular manifestions.[33,34] The major phenotypes include: 1) papules and pustules, 2) flushing, 3) telangiectasia, and 4) ocular manifestations.[33,34] In a systematic review and meta-analysis of 39 studies including more than 9000 patients, the proportion of erythematotelangiectatic rosacea was 57%, papulopustular rosacea, 43%, phymatous rosacea, 7%, and ocular rosacea, 11%.[29] Subtype distribution occurred equally among men and women except for phymatous rosacea, which was more prevalent in men.[29]

Table 1. National Rosacea Society: Rosacea Subtypes[30]

Subtype	Characteristics
Erythematotelangiectatic	Flushing and persistent central facial erythema with or without telangiectasia.
Papulopustular	Persistent central facial erythema with transient, central facial papules or pustules or both.
Phymatous	Thickening skin, irregular surface nodularities and enlargement. May occur on the nose, chin, forehead, cheeks, or ears.
Ocular	Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema.

Since rosacea is a chronic inflammatory condition that waxes and wanes, with many triggers, the goal of treatment is to resolve acute flares with rapid-acting treatments and maintain the results with lifestyle modification and prolonged combination therapy.[35] The avoidance of triggers, particularly ultraviolet light exposure, is critical for long-term improvement and disease control, and should be an essential component of patient education.[35] The fundamental key for successful management of rosacea is based on identification of the specific subtype, understanding the severity of presentation, and tailoring treatments to best meet the expectations of the patient.[35] When assessing treatment, patients' perception and acceptance of their facial appearance—including its impact on their emotional, social, and professional lives—may be important in determining the level of therapy.[36] Patient surveys have suggested that the psychosocial burden of rosacea may be substantial regardless of severity and that the goal of achieving an IGA of 0 for inflammatory papules and pustules may often be appropriate and feasible.[36] NICE cites an IGA scale that has been used in clinical trials of therapeutic agents for rosacea and is presented in **Table 2**.

Table 2. Investigator Global Assessment Scale for Rosacea[11]

Score	Grade	Clinical Description
0	Clear	No inflammatory lesions present, no erythema
1	Almost Clear	Very few small papules/pustules, very mild erythema
2	Mild	Few small papules/pustules, mild erythema
3	Moderate	Several small or large papules/pustules, moderate erythema
4	Severe	Numerous small and/or large papules/pustules, severe erythema

The major treatments for persistent facial erythema include topical alpha-adrenergic agonists (brimonidine or oxymetazoline) and light-based therapies (laser or intense pulsed light treatments).[37] The FDA-approved topical therapies for the treatment of persistent facial erythema of rosacea in adults include brimonidine topical gel, 0.33%, and oxymetazoline hydrochloride cream, 1% applied once daily.[36] Brimonidine may reduce facial erythema within 30 minutes of application and peak around 3 to 6 hours after application; the total duration of erythema reduction is 3-12 hours.[38] Compared to placebo, there is high-quality evidence for the efficacy of brimonidine in reducing erythema, while the quality of evidence for oxymetazoline is moderate.[38] There are no head-to-head comparisons of brimonidine and oxymetazoline.[38] Telangiectasias are best managed with laser or intense pulsed light treatments.[37] Telangiectasias are unlikely to improve with medications.[37]

Topical and systemic therapy are the mainstays of treatment for rosacea presenting with inflammatory papules and/or pustules.[37] Mild to moderate papulopustular features can often be treated with topical therapy.[36,37] The FDA-approved topical therapies for inflammatory papules/pustules of rosacea include azelaic acid, 15%; ivermectin cream, 1%; and metronidazole, 1% and 0.75%.[36] Depending on the formulation, the topical products are applied once or twice daily. When first-line treatments for inflammation are inadequate or when rosacea is more severe, off-label oral antibiotics or retinoids are sometimes used, although data are sparse for these treatments.[36] These may include tetracycline, doxycycline, minocycline, and oral isotretinoin.[36] Modified-release oral doxycycline

capsules, 40 mg (30 mg immediate release and 10 mg delayed release beads), were approved by the FDA for the treatment of inflammatory papules/pustules of rosacea that are severe or poorly responsive to topical therapy alone.[39] Duration of therapy is recommended for 12 to 16 weeks or longer based on response to therapy.[39] This formulation is a lower dosage than that of doxycycline used to treat infections, and has been associated with fewer adverse effects than the 100 mg dosing regimen.[36] Studies suggest that medications primarily used for papulopustular features of rosacea (e.g., topical antimicrobials, azelaic acid, and oral antibiotics) may improve rosacea-associated facial erythema.[37] However, no high-quality randomized trials have evaluated these therapies in patients without concomitant papules and pustules.[37] Topical and oral therapy are often initially prescribed in combination, followed by long-term use of a single therapy alone to maintain remission.[36]

For ocular rosacea, lid scrubs and warm compresses may help improve meibomian gland function, and topical antibiotics (e.g., topical erythromycin, azithromycin, metronidazole) or topical ivermectin may quell mild lid inflammation.[37] For moderate to severe ocular rosacea, short courses of oral tetracycline-class antibiotics, macrolide antibiotics, or metronidazole are often needed.[37] Topical cyclosporine drops may be additive in decreasing the topical inflammation in these patients.[36] Tissue hypertrophy, dilated follicles, and irregular nodular overgrowths are characteristic features of the phymatous skin changes of rosacea.[37] These changes most commonly affect the nose (rhinophyma), but may also affect other areas such as the chin, cheeks, and ears.[37] Laser ablation and surgical techniques can be used to debulk and recontour tissue distorted by phymatous changes.[37]

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

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

New Systematic Reviews:
Cochrane Review: Topical Interventions For Acne
A 2024 Cochrane Review evaluated the evidence on the efficacy and safety of topical therapies used in the treatment of acne vulgaris.[1] Literature was searched through December 2, 2021 for relevant systematic reviews.[1] Six systematic reviews with low risk of bias met the inclusion criteria.[1] The six reviews involved 40,910 people with acne from 275 trials and 1,316 people with acne scars from 37 trials.[1] The age of the participants ranged from 10 to 59 years.[1] No systematic review collected data for the following comparisons: topical antibiotics versus placebo or no treatment, topical retinoids versus placebo or no treatment, or topical retinoids versus topical antibiotics.[1] No high-certainty evidence for the effects of any therapy was identified.[1] The data for topical benzoyl peroxide, adapalene and clindamycin is summarized below.

Benzoyl Peroxide Versus Placebo or No Treatment

In 2 trials involving 1,012 participants over 12 weeks, benzoyl peroxide may reduce the total (mean difference (MD) -16.14, 95% confidence interval (CI) -26.51 to -5.78), inflammatory (MD -6.12, 95% CI -11.02 to -1.22), and non-inflammatory lesion counts (MD -9.69, 95% CI -15.08 to -4.29) when compared to placebo over 12 weeks, but the evidence is very uncertain (very low-certainty evidence).[1] Benzoyl peroxide may have little to no effect in improving participants' global self-assessment compared to placebo at 10 and 12 weeks (risk ratio (RR) 1.44, 95% CI 0.94 to 2.22; 2 trials, n=1,073; very low-certainty evidence).[1] Very low-certainty evidence suggested that benzoyl peroxide may improve IGA scores over 12 weeks (RR 1.77, 95% CI 1.37 to 2.28; 6 trials, n=4,110) compared to placebo.[1] Benzoyl peroxide may increase the risk of a less serious adverse event compared to placebo over 10 to 12 weeks (RR 1.46, 95% CI 1.01 to 2.11; 13 trials; n=4,287; very low-certainty evidence).[1]

Benzoyl Peroxide Versus Topical Retinoids

Benzoyl peroxide may increase the percentage change in total lesion count compared to adapalene (MD 10.8, 95% CI 3.38 to 18.22; 1 trial, 205 participants, 12 weeks; very low-certainty evidence).[1] When compared to adapalene, benzoyl peroxide may have little to no effect on the following outcomes: percentage change in inflammatory lesion counts (MD -7.7, 95% CI -16.46 to 1.06; 1 trial, 142 participants, 11 weeks; very low-certainty evidence), percentage change in non-inflammatory lesion counts (MD -3.9, 95% CI -13.31 to 5.51; 1 trial, 142 participants, 11 weeks; very low-certainty evidence), participant's global self-assessment (RR 0.96, 95% CI 0.86 to 1.06; 4 trials, 1123 participants, 11 to 12 weeks; low-certainty evidence), IGA score (RR 1.16, 95% CI 0.98 to 1.37; 3 trials, 1965 participants, 12 weeks; low-certainty evidence), and incidence of a less serious adverse event (RR 0.77, 95% CI 0.48 to 1.25, 1573 participants, 5 trials, 11 to 12 weeks; very low-certainty evidence).[1]

Benzoyl Peroxide Versus Topical Antibiotics

When compared to clindamycin, benzoyl peroxide may have little to no effect on the following outcomes: total lesion counts (MD -3.50, 95% CI -7.54 to 0.54; 1 trial, 641 participants, 12 weeks; very low-certainty evidence), inflammatory lesion counts (MD -1.20, 95% CI -2.99 to 0.59; 1 trial, 641 participants, 12 weeks; very low-certainty evidence), non-inflammatory lesion counts (MD -2.4, 95% CI -5.3 to 0.5; 1 trial, 641 participants, 12 weeks; very low-certainty evidence), participant's global self-assessment (RR 0.95, 95% CI 0.68 to 1.34; 1 trial, 240 participants, 10 weeks; low-certainty evidence), IGA score (RR 1.10, 95% CI 0.83 to 1.45; 2 trials, 2277 participants, 12 weeks; very low-certainty evidence), and incidence of a less serious adverse event (RR 1.27, 95% CI 0.98 to 1.64; 5 trials, 2842 participants, 10 to 12 weeks; low-certainty evidence).[1]

This Cochrane review summarizes the evidence from 6 systematic reviews regarding the effects of topical therapy (benzoyl peroxide, adapalene, clindamycin) for treating acne and acne scars. The evidence regarding the effects of most interventions is very uncertain.[1] The studies included in this review had limited observations of serious adverse effects and quality of life.[1] There was insufficient high-quality evidence to summarize the evidence for topical retinoids and topical antibiotics, specifically these 2 classes of drugs compared with placebo or no treatment and with each other.[1]

Cochrane Review: Interventions For Rosacea

A 2015 Cochrane review assessed the efficacy and safety of treatments for rosacea.[5] Literature was searched through July, 2014 for RCTs conducted in people with moderate to severe rosacea.[5] A total of 106 studies, comprising 13,631 participants met inclusion criteria.[5] Sample sizes of 30 to 100 participants and study duration of 2 to 3 months were most common.[5] More women than men were included, mean age of 48.6 years, and the majority had papulopustular rosacea, followed by erythematotelangiectatic rosacea.[5]

Topical interventions included: metronidazole, azelaic acid, ivermectin, or brimonidine.[5] Systemic interventions included: oral antibiotics and combinations with topical treatments or other systemic treatments, i.e. isotretinoin.[5] Several studies evaluated laser or light-based treatment.[5] The majority of studies (57/106) were assessed as unclear risk of bias, 37 studies were assessed as high risk of bias, and 12 trials were at low risk of bias.[5] The quality of the body of evidence was rated moderate to high for most outcomes, but for some outcomes low- to very low-quality.[5]

Eleven studies assessed the primary outcome of change in quality of life, 52 studies evaluated participant-assessed changes in rosacea severity and almost all studies addressed adverse events, although often only limited data were provided.[5] In most comparisons there were no statistically significant differences in number of adverse events, most events were mild and transient.[5] Five RCTs evaluated treatments for ocular rosacea.[5] Physician assessments including IGA scores, lesion counts, and erythema were evaluated in three-quarters of the studies, but time needed for improvement and duration of remission were incompletely or not reported.[5]

Data for several outcomes could only be pooled for topical metronidazole and azelaic acid.[5] Both were shown to be more effective than placebo in managing papulopustular rosacea (moderate-quality evidence for metronidazole and high-quality evidence for azelaic acid).[5] Pooled data from physician assessments in 3 trials demonstrated that metronidazole was more effective compared to placebo (RR 1.98, 95% CI 1.29 to 3.02).[5] Four trials provided data on participants' assessments, showing that azelaic acid was more effective than placebo (RR 1.46, 95% CI 1.30 to 1.63).[5] Improvements tended to appear after 3 to 6 weeks.[5] With metronidazole, very few people experienced mild itching, skin irritation and dry skin.[5] For some people, azelaic acid caused mild burning, stinging or irritation.[5]

Two studies showed a statistically significant and clinically important improvement in favor of topical ivermectin when compared to placebo (high-quality evidence).[5] Participants' assessments in these studies showed a RR of 1.78 (95% CI 1.50 to 2.11) and RR of 1.92 (95% CI 1.59 to 2.32),which were supported by physicians' assessments.[5] Topical ivermectin appeared to be slightly more effective than topical metronidazole for papulopustular rosacea, based on one study, for improving quality of life and participant and physician assessed outcomes (high-quality evidence for these outcomes).[5]

Topical brimonidine in 2 studies was more effective than vehicle in reducing erythema in rosacea at all time points over 12 hours (high-quality evidence).[5] At 3 hours the participants' assessments had a RR of 2.21 (95% CI 1.52 to 3.22) and RR of 2.00 (95% CI 1.33 to 3.01) in favor of brimonidine.[5] Physicians' assessments confirmed these data. There was no rebound or worsening of erythema after treatment cessation.[5] Topical clindamycin phosphate combined with tretinoin was not considered to be effective for improving rosacea severity compared to placebo (moderate-quality evidence).[5] Compared with artificial tears, topical cyclosporin ophthalmic emulsion demonstrated effectiveness and improved quality of life for people with ocular rosacea (low-quality evidence).[5]

Of the comparisons assessing oral treatments for papulopustular rosacea, there was moderate-quality evidence that tetracycline was effective but this was based on 2 dated studies completed in 1966 and 1971 and of short duration (6 weeks).[5] Physician-based assessments in two trials indicated that doxycycline appeared to be significantly more effective than placebo (RR 1.59, 95% CI 1.02 to 2.47 and RR 2.37, 95% CI 1.12 to 4.99; high-quality evidence).[5] There was no statistically significant difference in effectiveness between 100 mg and 40 mg doxycycline, but there was evidence of fewer adverse effects (e.g., diarrhea, nausea) with the lower doxycycline dose (RR 0.25, 95% CI 0.11 to 0.54; low-quality evidence).[5] There was very low-quality evidence from one study (assessed at high risk of bias) that doxycycline 100 mg was as effective as azithromycin.[5] Low dose minocycline (45 mg) was effective for papulopustular rosacea (low-quality evidence).[5]

Oral tetracycline was compared with topical metronidazole in 4 studies and showed no statistically significant difference between the 2 treatments for any rosacea outcome (low- to moderate-quality evidence).[5] Low dose isotretinoin was considered by both the participants (RR 1.23, 95% CI 1.05 to 1.43) and physicians (RR 1.18, 95% CI 1.03 to 1.36) to be slightly more effective than doxycycline 50-100 mg (high-quality evidence) for treating pimples and pustules associated with rosacea.[5]

In summary, the authors concluded:

- There was high-quality evidence to support the effectiveness and safety of brimonidine topical gel for reducing erythema over 12 hours after application in the management of persistent erythema in rosacea.[5] The effect of brimonidine was temporary.[5]
- For management of papulopustular rosacea, topical metronidazole, azelaic acid, and ivermectin, or oral anti-inflammatory dose doxycycline (40 mg), tetracycline and isotretinoin 0.3 mg/kg appear to be effective and safe for short-term use (moderate- to high-quality evidence).[5] It still needs to be established whether azelaic acid is more effective than topical metronidazole, but topical ivermectin appeared to be slightly more effective than topical metronidazole.[5] There is evidence that 40 mg doxycycline is at least as effective as 100 mg, with evidence of fewer adverse effects (low-quality evidence).[5] There is low-quality evidence for the effectiveness and safety of low dose minocycline 45 mg and very low-quality evidence of azithromycin for this rosacea subtype.[5] There is no clear evidence that any one of these treatments, or any combination of treatments, has a particular advantage in terms of higher remission rates or fewer adverse effects.[5]
- There was insufficient evidence to address the treatment of phymatous rosacea.[5]
- For ocular rosacea, cyclosporin 0.05% ophthalmic emulsion was shown to be more beneficial than artificial tears (low-quality evidence).[5] Further studies on treatment of ocular rosacea are warranted.[5]
- Time needed to response and response duration should be addressed more completely, with more rigorous reporting of adverse events.[5]

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[40-45] wrong study design of included trials (e.g., observational),[46] comparator (e.g., no control or placebo-controlled),[38,47-51] or outcome studied (e.g., non-clinical).

New Guidelines:

<u>High Quality Guidelines:</u>

Acne Guidance

Canada's Drug Agency: Reimbursement Recommendation for Clascoterone

In 2025 CDA issued reimbursement recommendations for the topical treatment of acne vulgaris with clascoterone.[3] Evidence from 2 clinical trials demonstrated that clascoterone increased the rate of treatment success (assessed using a measure of overall acne severity) compared with its vehicle cream (without active ingredient).[3] However, based on the evidence reviewed, the Canadian Drug Expert Committee (CDEC) could not determine if clascoterone would address the unmet needs (improving skin clearance, reducing scarring, and improving quality of life) relative to other active treatments.[3] The results for clinically relevant skin clearance outcomes, (change from baseline in noninflammatory lesion counts, inflammatory lesion counts, and total lesion counts), were statistically significant in the pivotal trials compared to the vehicle cream. However, the evidence was uncertain because of a high level of missing data, and the results did not reach the threshold for a minimally clinical important difference compared to the vehicle cream.[3] There was a lack of direct comparative data to assess how clascoterone compares to other acne treatments in terms of efficacy and tolerability.[3] For these reasons, the CDA recommends that clascoterone not be reimbursed for the topical treatment of acne vulgaris in patients aged 12 years and older.[3]

Canada's Drug Agency: Reimbursement Recommendation for Clindamycin/Benzoyl Peroxide/Adapalene Triple Therapy

The CDA provided reimbursement recommendations for the triple combination topical clindamycin/benzoyl peroxide/adapalene gel (CABTREO) in November 2024.[4] Evidence from 2 clinical trials showed that treatment with clindamycin/benzoyl peroxide/adapalene gel increased the rate of treatment success (measured using an acne severity scale) and reduced the number of inflammatory and noninflammatory lesions after 12 weeks of treatment compared with its vehicle gel in people with moderate to severe acne vulgaris.[4] The treatment effect of clindamycin/benzoyl peroxide/adapalene gel on acne, compared with topical treatments that are a combination of 2 active ingredients, was uncertain.[4]

Based on an assessment of the health economic evidence by the CDEC, clindamycin/benzoyl peroxide/adapalene does not represent good value to the health care system at the public list price.[4] The committee determined that there is not enough evidence to justify a greater cost for the triple combination product compared to topical therapies currently reimbursed by participating plans.[4] The CDA recommends that clindamycin/benzoyl peroxide/adapalene gel be reimbursed by public drug plans for the topical treatment of acne vulgaris in patients 12 years of age and older only if pricing for this drug can be negotiated with participating plans so that the cost of treatment does not exceed other topical therapies.[4]

National Institute For Health And Care Excellence Guideline On Acne Vulgaris: Management

NICE updated guidance for acne vulgaris management in 2023.[2] First-line treatment options with advantages and disadvantages are presented in **Table 2**. The current guidelines recommend topical benzoyl peroxide combined with topical clindamycin for mild to moderate acne, and combined topical adapalene with topical benzoyl peroxide or topical azelaic combined with oral doxycycline for moderate to severe acne.[2] Additionally, for any severity of acne, either topical adapalene combined with topical benzoyl peroxide or topical retinoids combined with topical clindamycin may be used, but antibiotic monotherapy or topical products plus oral antibiotics are not recommended. People should be offered a 12-week trial of one of the therapeutic options in **Table 3.**[2]

Table 3. National Institute for Health and Care Excellence: First-Line Recommendations for Treatment of Acne Vulgaris[2]

Acne Severity	Treatment	Advantages	Disadvantages
Any Severity	Fixed combination of topical adapalene with topical benzoyl peroxide	• Topical • Does not contain antibiotics	• Not for use during pregnancy • Use with caution during breastfeeding • Can cause skin irritation, photosensitivity, and bleaching of hair and fabrics
Any Severity	Fixed combination of topical tretinoin with topical clindamycin	• Topical	• Not for use during pregnancy or breastfeeding • Can cause skin irritation
Mild to Moderate	Fixed combination of topical benzoyl peroxide with topical clindamycin	• Topical • Can be used with caution during pregnancy and breastfeeding	• Can cause skin irritation, photosensitivity, and bleaching of hair and fabrics
Moderate to Severe	Fixed combination of topical adapalene with topical benzoyl peroxide plus oral doxycycline	• Oral components may be effective in treating affected areas that are difficult to reach with topical treatment (such as the back) • Treatment with adequate courses of standard therapy with systemic antibiotics and topical therapy is a requirement for subsequent oral tretinoin, which is only recommended for severe acne	• Not for use during pregnancy or breastfeeding or under the age of 12 years • Topical adapalene and benzoyl peroxide can cause skin irritation, photosensitivity, and bleaching of hair and fabrics • Oral antibiotics may cause systemic side effects and antimicrobial resistance • Oral tetracyclines can cause photosensitivity

Moderate to Severe	Topical azelaic acid plus oral doxycycline	• Oral components may be effective in treating affected areas that are difficult to reach with topical treatment (such as the back) • Treatment with adequate courses of standard therapy with systemic antibiotics and topical therapy is a requirement for subsequent oral tretinoin, which is only recommended for severe acne	• Not for use during pregnancy or breastfeeding or under the age of 12 years • Oral antibiotics may cause systemic side effects and antimicrobial resistance • Oral tetracyclines can cause photosensitivity

Other recommendations include:

- Consider topical benzoyl peroxide monotherapy as an alternative treatment to the options in **Table 2** if these treatments are contraindicated, or the person wishes to avoid using a topical retinoid or an antibiotic (topical or oral).[2]
- For people with moderate to severe acne who cannot tolerate or have contraindications to oral doxycycline, consider replacing these medications in the combination treatments in **Table 2** with trimethoprim, or an oral macrolide (e.g., erythromycin).[2]
- To reduce the risk of skin irritation associated with topical treatments, such as benzoyl peroxide or retinoids, start with alternate-day or short contact application (for example washing off after an hour). If tolerated, progress to using a standard, once daily application.[2]
- When discussing treatment choices in a person with childbearing potential be sure to stress that topical retinoids and oral tetracyclines are contraindicated during pregnancy and that effective contraception should be used during acne treatment with these agents.[2]
- If a person receiving treatment of acne wishes to use hormonal contraception, consider using the combined oral contraceptive pill in preference to the progesterone-only pill.[2]
- Consider oral tretinoin for people older than 12 years of age who have a severe form of acne that is resistant to adequate courses of standard therapy with systemic antibiotics and topical therapy. Severe forms of acne include: nodulo-cystic acne, acne conglobata, acne fulminans, and acne at risk of permanent scarring.[2]
- Do not use the following to treat acne: monotherapy with a topical antibiotic, monotherapy with an oral antibiotic, or a combination of an oral and topical antibiotic.[2]
- Review first-line treatments at 12 weeks and:
    - Assess whether the person's acne has improved, and whether they have any side effects.
    - In people whose treatment includes an oral antibiotic, if their acne has completely cleared consider stopping the antibiotic but continuing topical treatment.
    - In people whose treatment includes an oral antibiotic, if their acne has improved but not completely cleared, consider continuing the oral antibiotic, alongside topical treatment, for up to 12 more weeks.[2]
- If acne fails to respond adequately to a 12-week course of first-line treatment option and at review the severity is:
    - Mild to Moderate: Offer another option from the table of treatment choices.
    - Moderate to Severe: And the treatment did not include an oral antibiotic, offer another option which includes an oral antibiotic.
    - Moderate to Severe And the treatment included an oral antibiotic, consider referral to a dermatologist.[2]
- If mild to moderate acne fails to respond adequately to 2 different 12-week treatment courses, consider referral to a dermatologist.[2]

Rosacea Guidance

Update on the Management of Rosacea from the American Acne & Rosacea Society

In 2019 the AARS published rosacea management recommendations based upon available evidence and clinical experience.[6] In all cases, proper skin care, photoprotection, and avoidance of patient-specific rosacea triggers are suggested.[6] Recommendations include initial use of topical metronidazole or topical azelaic acid concurrently with oral doxycycline for treatment of severe papulopustular rosacea with transition to topical therapy alone after adequate response is achieved; topical brimonidine and topical ivermectin for treatment of papulopustular rosacea with diffuse persistent facial erythema of at least moderate severity; and combination treatment with potassium titanyl phosphate laser and topical brimonidine for diffuse persistent facial erythema of rosacea.[6] Recommendations and quality of evidence are presented in **Table 4**.

Most of the evidence was evaluated as "B" or moderate-quality, based upon systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings; lower-quality clinical trial. Low-quality evidence (rated as "C") was based upon consensus guidelines; usual practice, expert opinion, or case series—limited trial data. [6]

Table 4. American Acne and Rosacea Society Recommendations for Rosacea Management[6]

Rosacea Presentation	Management Options	Quality of Evidence (A,B,C)	Evidence Comments
Persistent central facial erythema without PP lesions	• Topical alpha-agonist: brimonidine or oxymetazoline • Intense pulsed light, potassium titanyl phosphate, crystal laser, or pulsed-dye laser	B	• More data are needed on optimal use of specific device therapies and topical alpha-agonist therapy in combination. • Combination of an oral and topical agent that reduce PP lesions and perilesional erythema based on severity; topical alpha-agonist used for persistent background erythema caused by fixed dilated vasculature.
Diffuse central facial erythema with PP lesions	• Topical metronidazole • Topical azelaic acid • Topical ivermectin • Oral tetracyclines • Topical alpha-agonists • Oral isotretinoin	B	• Sub-antibiotic dose doxycycline is the preferred initial oral therapy option due to absence of bacterial selection pressure. • Oral azithromycin is an alternative option if an oral tetracycline is not effective or poorly tolerated (caution in some patients due to potential cardiac risks). • Oral isotretinoin for refractory disease (transition to intermittent therapy after initial control). • Other alternative topical agents include sulfacetamide-sulfur, calcineurin inhibitors, retinoids, and permethrin (limited data available on these agents).
Flushing of rosacea (acute-subacute intermittent vasodilation)	• Flushing is better prevented than treated via avoidance of known triggers, such as sun exposure and photoprotection. • Use of low-dose oral drugs with vasoconstrictive properties, including mirtazapine, propranolol, or carvedilol.	B	• Data are limited on the management of flushing of rosacea. • Limited data exist on topical therapies. • Some botanicals and natural ingredients might improve facial redness and flushing (niacinamide, parthenolide-free extract of feverfew (*Tanacetum parthenium)*, licorice derivatives, chamomile, green tea) based on preliminary small studies. • An anti-inflammatory cleanser night mask combination was found to markedly reduce facial redness (limited data).
Ocular Rosacea	• Lid hygiene, sunglasses, eye lubrication formulations	B	• Data are based on clinical experience, case reports, and small studies • Topical corticosteroids for short-term therapy but avoid chronic use

	• Cyclosporin ophthalmic emulsion (3-month, randomized, controlled trial [n=37]) • Topical metronidazole or ivermectin (blepharitis; applied to external eyelid skin) • Oral doxycycline, erythromycin, or azithromycin		• Sub-antibiotic dose doxycycline suggested for long-term therapy
Granulomatous Rosacea	• Oral tetracyclines • Topical pimecrolimus (case reports) • Oral isotretinoin (0.7mg/kg/day for 6 months) • Oral dapsone • Intense pulsed-dye laser (case report) • Photodynamic therapy (case report) • Topical brimonidine	C	• No current standard of treatment; limited data based mostly on case reports • Oral isotretinoin may produce improvement without recurrence
Phymatous Rosacea	Surgical therapy for fully developed phymatous changed (carbon dioxide laser, erbium-doped yttrium aluminum garnet (YAG) laser, electrosurgery, dermabrasion	C	• Treatment selection dependent on stage of development (early or fibrotic) and extent of inflammation (active or burnt out) • Oral isotretinoin might improve early soft phymatous changes due to sebaceous hyperplasia
Abbreviations: PP = papulopustular			

Canada's Drug Agency: Topical Ivermectin, Oral Doxycycline 40 mg, and Topical Azelaic Acid

- In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH), now known as the CDA, issued recommendations for topical ivermectin 1% in the treatment of inflammatory rosacea lesions.[7] Two RCTs demonstrated that ivermectin 1% once daily was associated with a statistically significantly greater reduction in the number of inflammatory lesions and a statistically significantly higher success rate than vehicle-treated patients with rosacea.[7] One RCT demonstrated that ivermectin 1% was associated with a statistically significantly greater percentage reduction in the number of inflammatory lesions (−83.0% versus −73.7%) and a statistically significantly higher success rate (84.9% versus 75.4%) compared with metronidazole (0.75% cream applied twice daily); however, the clinical relevance of these differences is uncertain.[7] The CDEC recommended coverage of topical ivermectin for treatment of moderate to severe papulopustular rosacea if the drug plan cost for ivermectin did not exceed the drug plan cost of other topical rosacea treatments.[7]

- In 2013, CADTH issued recommendations for oral doxycycline monohydrate 40 mg modified-release (MR) capsules.[8] The CDEC considered the comparative benefit of doxycycline 40 mg MR capsules to be uncertain due to limitations in the design and analysis of a single RCT that compared doxycycline 40 mg MR capsules with doxycycline 100 mg capsules in adults with inflammatory lesions (papules and pustules) of rosacea.[8] For this reasons, the CDEC recommended that doxycycline 40 mg MR capsules not be reimbursed for the treatment of adults with rosacea.[8]

- In 2011 CADTH issued recommendations for topical azelaic aid 15% gel in management of papulopustular rosacea.[9] In 2 RCTs, azelaic acid 15% gel had similar efficacy compared with metronidazole as either 0.75% or 1% gel for patients with mild to moderate papulopustular rosacea in terms of reduced lesion count and IGA severity.[9] The CDEC recommended coverage of topical azelaic acid 15% gel for management of rosacea.[9]

National Institute for Health and Care Excellence: Topical Brimonidine Gel and Ivermectin

- In 2014, NICE reviewed the evidence for the use of topical brimonidine gel in management of facial erythema of rosacea.[10] In 2 short-term (4 weeks of treatment and 4 weeks of follow-up) RCTs (n=553) brimonidine tartrate gel was statistically significantly more effective than vehicle gel in reducing erythema in people with rosacea and moderate to severe erythema.[10] Success rates (defined as 2-grade reduction in severity of erythema assessed by both patients and clinicians) were just 25% to 30% with brimonidine gel compared with 10% for vehicle gel at day 29.[10] Efficacy endpoint for erythema of rosacea are not clearly established and the scales used in these clinical trials were subjective judgements, not objective measures, therefore, defining what a clinically important change on these scales is difficult.[10] The most commonly reported adverse effects with brimonidine gel included erythema, pruritus, flushing, and skin burning sensation.[10] Rosacea is a chronic condition and although brimonidine gel has a transient effect on erythema, it does not alter the course of the disease or have any effect on other features of rosacea such as telangiectasia or inflammatory papules.[10]

  NICE did not issue any recommendations for the use of brimonidine gel in rosacea but suggested that it may be an option for adults with moderate to severe rosacea and facial erythema. Specialists suggested that some people may only use brimonidine gel on days when they are particularly self-conscious about their appearance.[10] Before continuing long-term treatment with brimonidine gel, consideration should be given to how treatment efficacy can be assessed given the subjective nature of efficacy outcomes and the low response rates seen in clinical trials.[10] Specialists advised that it is important to ensure lifestyle recommendations, such as using sunscreen and avoiding triggers are optimized before initiating brimonidine gel.[10]

- In 2016, NICE reviewed evidence for the use to topical ivermectin cream in treatment of inflammatory lesions associated with papulopustular rosacea.[11] In 2 RCTs (n=1371) ivermectin cream was statistically significantly more effective than vehicle cream in improving rosacea severity score (IGA success rate [score of 0 or 1]: 39% vs. 15%) and reducing mean inflammatory lesion count (8 fewer lesions with ivermectin vs vehicle) over 4 weeks.[11] In another RCT (n=962), ivermectin was superior to metronidazole cream at reducing lesion count by 10% and improving rosacea severity score over 16 weeks (IGA success rate 85% vs. 75%, $p<0.001$).[11] There are no published studies comparing ivermectin with azelaic acid in patients with rosacea.[11] Local adverse events including skin burning sensation, skin irritation, pruritis and dry skin are common, although these are mostly transient, mild to moderate in severity and usually decrease when treatment is continued.[11]

  NICE did not issue any recommendations for ivermectin cream in managing inflammatory lesions due to rosacea but suggested that mild to moderate papulopustular rosacea is usually treated with topical metronidazole or azelaic acid with moderate or severe papulopustular rosacea often managed with oral antibiotics (i.e., tetracycline, erythromycin, doxycycline).[11] Metronidazole cream is generally considered first-line topical treatment for rosacea.[11] Azelaic acid may be more effective than metronidazole, but is often less well tolerated. Ivermectin may be slightly more effective than metronidazole with a comparable incidence of adverse events.[11] At the time of the review, ivermectin cream was more costly than metronidazole or azelaic acid, so NICE recommended that local decision makers consider the available evidence on efficacy and safety as well as cost when making decisions about using ivermectin cream or another topical agent for papulopustular rosacea.[11]

<u>Additional Guidelines for Clinical Context:</u>

American Academy of Dermatology: Guidelines Of Care For The Management Of Acne Vulgaris

Based on conflict of interest methodology, this guideline is not of high quality as over half of the work group (15/20) received grants, funding, stock options, or honoraria from pharmaceutical manufacturers.[24] Less than half of the work group (5/20 members) had no relevant relationships to disclose.[24] The AAD did not address how conflicts of interests of the guideline panel were mitigated.

The AAD updated recommendations for management of acne in 2024.[24] Strong recommendations are made for treating acne with benzoyl peroxide, topical retinoids, topical antibiotics, and oral doxycycline.[24] Oral isotretinoin is strongly recommended for acne that is severe, causing psychosocial burden or scarring, or failing standard oral or topical therapy.[24] Conditional recommendations are made for topical clascoterone, salicylic acid, and azelaic acid, as well as for oral minocycline, sarecycline, combined oral contraceptive pills, and spironolactone.[24] Combining topical therapies with multiple mechanisms of action, limiting systemic antibiotic use, combining systemic antibiotics with topical therapies, and adding intralesional corticosteroid injections for larger acne lesions are recommended as good practice statements.[24] A summary of recommendations and quality of evidence is provided in **Table 5**.

Table 5. American Academy of Dermatology Guidance for Acne Vulgaris Management in Adults, Adolescents, and Preadolescents (older than 9 years)[24]

Treatment	Strength of Recommendation	Certainty of Evidence
Topical Agents		
When managing acne with topical medications, we recommend multimodal therapy combining multiple mechanisms of action.	Good Practice Statement	N/A
For patients with acne, we recommend benzoyl peroxide.	Strong	Moderate
For patients with acne, we recommend topical retinoids.	Strong	Moderate
For patients with acne, we recommend topical antibiotics. Remark: Topical antibiotic monotherapy is not recommended.	Strong	Moderate
For patients with acne, we conditionally recommend clascoterone.	Conditional*	High
For patients with acne, we conditionally recommend salicylic acid.	Conditional	Low
For patients with acne, we conditionally recommend azelaic acid.	Conditional	Moderate
For patients with acne, we recommend fixed dose combination topical retinoid with topical antibiotic. Remark: Concomitant use of benzoyl peroxide is recommended to prevent the development of antibiotic resistance.	Strong	Moderate
For patients with acne, we recommend fixed dose combination topical retinoid with benzoyl peroxide.	Strong	Moderate
Systemic Antibiotics		
For patients with acne, we recommend doxycycline.	Strong	Moderate
For patients with acne, we conditionally recommend minocycline.	Conditional	Moderate
For patients with acne, we conditionally recommend sarecycline	Conditional***	High
For patients with acne, we conditionally recommend doxycycline over azithromycin.	Conditional	Low
For patients with acne, we recommend limiting use of systemic antibiotics, when possible, to reduce the development of antibiotic resistance and other antibiotic associated complications.	Good Practice Statement	N/A
It is recommended that systemic antibiotics are used concomitantly with benzoyl peroxide and other topical therapy.	Good Practice Statement	N/A
Hormonal Agents		
For patients with acne, we conditionally recommend combined oral contraceptive pills.	Conditional**	Moderate
For patients with acne, we conditionally recommend spironolactone. Remark: Potassium monitoring is not needed in healthy patients. However, consider potassium testing for those with risk factors for hyperkalemia (e.g., older age, medical comorbidities, medications).	Conditional	Moderate

For patients with larger acne papules or nodules, we recommend intralesional corticosteroid injections as an adjuvant therapy. Remark: Intralesional corticosteroid injections should be used judiciously for patients who are at risk of acne scarring and/or for rapid improvement in inflammation and pain. Using a lower concentration and volume of corticosteroid can minimize the risks of local corticosteroid adverse events.	Good Practice Statement	N/A
Isotretinoin		
For patients with severe acne or for patients who have failed standard treatment with oral or topical therapy, we recommend isotretinoin. Remark: Acne patients with psychosocial burden or scarring should be considered as having severe acne and to be candidates for isotretinoin. For patients undergoing treatment with isotretinoin, monitoring of LFTs and lipids should be considered, but CBC monitoring is not needed in healthy patients. Population-based studies have not identified increased risk of neuropsychiatric conditions or inflammatory bowel disease in acne patients undergoing treatment with isotretinoin. For persons of childbearing potential, pregnancy prevention is mandatory.	Good Practice Statement	N/A
For patients with severe acne, we conditionally recommend traditional daily dosing of isotretinoin over intermittent dosing of isotretinoin.	Conditional	Low
Physical Modalities		
For patients with acne, we conditionally recommend against adding pneumatic broadband light to adapalene 0.3% gel.	Conditional	Low
*Conditional recommendations were made for clascoterone and sarecycline due to high current cost of treatment that may impact equitable acne treatment access. **Conditional recommendation was made for combined oral contraceptive pills due to the variability in patient values and preferences related to contraception and hormonal medications. ***Sarecycline is currently not available to Oregon Health Plan members due to its current marketing status as non-rebatable.		
Abbreviations: N/A = not applicable		

After review, 2 clinical guidelines were excluded due to poor quality.[36,52]

New Formulations:

- In July 2021, the FDA approved a new combination formulation of tretinoin 0.1% and benzoyl peroxide 3% (TWYNEO) cream indicated for topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older.[12] The safety and efficacy of this combination product was evaluated in 2 vehicle-controlled RCTs (n=858) conducted over 12 weeks in people 9 years and older with moderate to severe facial acne vulgaris.[12] By week 12 the absolute change in inflammatory lesion count from baseline and IGA success (defined as a score of 0 [clear] or 1 [almost clear] were statistically significantly improved with tretinoin/benzoyl peroxide compared to vehicle.[12]

- In October 2023, the FDA approved a triple combination of clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1% (CABTREO) gel indicated for the topical treatment of acne vulgaris in adults and pediatric patients aged 12 years and older.[13] The safety and efficacy of this combination product was evaluated in 2 vehicle-controlled RCTs (n=363) conducted over 12 weeks in people 10 years and older with moderate to severe facial acne vulgaris.[13] By week 12, more patients treated with clindamycin/adapalene/benzoyl peroxide achieved statistically significant improvement in lesion count and treatment success on the Evaluator's Global Severity Score (EGSS) of clear (0) or almost clear (1) compared to vehicle.[13]

- A new oral formulation of minocycline 40 mg (EMROSI) received FDA approval in November 2024.[14] This is a tetracycline-class drug indicated to treat inflammatory lesions (papules and pustules) of rosacea in adults.[14] This minocycline formulation has not been evaluated in the treatment or prevention of infections.[14] To reduce development of drug-resistant bacteria and maintain effectiveness of other antibiotics, use minocycline 40 mg only as indicated.[14] The safety and efficacy of minocycline 40 mg extended-release capsules was assessed in 2 placebo-controlled RCTs (n=653) conducted over 16 weeks in adults with moderate to severe papulopustular rosacea.[14] By week 16 the absolute change in inflammatory lesion count from baseline and IGA success (defined as a score of 0 [clear] or 1 [almost clear] were statistically significantly improved with minocycline compared to placebo.[14]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[53]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Adapalene/Benzoyl Peroxide	EPIDUO FORTE	4/2022	Contraindications	EPIDUO FORTE is contraindicated in patients with a history of hypersensitivity reactions to benzoyl peroxide or any components of the formulation in EPIDUO FORTE.

Randomized Controlled Trials:

A total of 43 citations were manually reviewed from the initial literature search. After further review, 43 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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ACNE PRODUCTS

Generic	Brand	Route	Form	PDL	OTC
adapalene	ADAPALENE	TOPICAL	CREAM (G)	Y	F
adapalene	DIFFERIN	TOPICAL	CREAM (G)	Y	F
adapalene	ADAPALENE	TOPICAL	GEL (GRAM)	Y	F
adapalene	ADAPALENE	TOPICAL	GEL (GRAM)	Y	O
adapalene	DIFFERIN	TOPICAL	GEL (GRAM)	Y	O
adapalene	ADAPALENE	TOPICAL	GEL W/PUMP	Y	F
adapalene	DIFFERIN	TOPICAL	GEL W/PUMP	Y	F
adapalene	DIFFERIN	TOPICAL	LOTION	Y	F
adapalene/benzoyl peroxide	ADAPALENE-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y	F
azelaic acid	AZELAIC ACID	TOPICAL	GEL (GRAM)	Y	F
azelaic acid	FINACEA	TOPICAL	GEL (GRAM)	Y	F
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	Y	O
benzoyl peroxide	PANOXYL	TOPICAL	CLEANSER	Y	O
benzoyl peroxide	ACNE MEDICATION	TOPICAL	GEL (GRAM)	Y	O
benzoyl peroxide	BENZAC W 10	TOPICAL	GEL (GRAM)	Y	F
benzoyl peroxide	BENZAC W 2.5	TOPICAL	GEL (GRAM)	Y	F
benzoyl peroxide	BENZAC W 5	TOPICAL	GEL (GRAM)	Y	F
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y	O
benzoyl peroxide	ACNE MEDICATION	TOPICAL	LOTION	Y	O
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	LOTION	Y	O
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL (GRAM)	Y	F
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y	F
clindamycin phos/benzoyl perox	NEUAC	TOPICAL	GEL (GRAM)	Y	F
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	TOPICAL	GEL W/PUMP	Y	F
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	Y	F
clindamycin phosphate	CLINDACIN	TOPICAL	FOAM	Y	F
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	FOAM	Y	F
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL (GRAM)	Y	F
clindamycin phosphate	CLEOCIN T	TOPICAL	LOTION	Y	F
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	LOTION	Y	F
clindamycin phosphate	CLINDACIN ETZ	TOPICAL	MED. SWAB	Y	F
clindamycin phosphate	CLINDACIN P	TOPICAL	MED. SWAB	Y	F
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	MED. SWAB	Y	F

clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	SOLUTION	Y	F
clindamycin/tretinoin	CLINDAMYCIN PHOS-TRETINOIN	TOPICAL	GEL (GRAM)	Y	F
dapsone	DAPSONE	TOPICAL	GEL (GRAM)	Y	F
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	GEL (GRAM)	Y	F
erythromycin base in ethanol	ERY	TOPICAL	MED. SWAB	Y	F
erythromycin base in ethanol	ERYTHROMYCIN	TOPICAL	SOLUTION	Y	F
erythromycin/benzoyl peroxide	ERYTHROMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL (GRAM)	Y	F
isotretinoin	ABSORICA	ORAL	CAPSULE	Y	F
isotretinoin	AMNESTEEM	ORAL	CAPSULE	Y	F
isotretinoin	CLARAVIS	ORAL	CAPSULE	Y	F
isotretinoin	ISOTRETINOIN	ORAL	CAPSULE	Y	F
isotretinoin	ZENATANE	ORAL	CAPSULE	Y	F
sulfacetamide sodium	SULFACETAMIDE SODIUM	TOPICAL	SUSPENSION	Y	F
tretinoin	TRETINOIN	TOPICAL	CREAM (G)	Y	F
tretinoin	TRETINOIN	TOPICAL	GEL (GRAM)	Y	F
adapalene/benzoyl peroxide	ADAPALENE-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	N	F
adapalene/benzoyl peroxide	EPIDUO FORTE	TOPICAL	GEL W/PUMP	N	F
azelaic acid	FINEVIN	TOPICAL	CREAM (G)	N	F
azelaic acid	FINACEA	TOPICAL	FOAM	N	F
benzoyl peroxide	BENZOYL PEROXIDE	TOPICAL	CLEANSER	N	O
benzoyl peroxide	BPO	TOPICAL	TOWELETTE	N	O
clascoterone	WINLEVI	TOPICAL	CREAM (G)	N	F
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	TOPICAL	GEL W/PUMP	N	F
clindamycin phos/skin clnsr 19	CLINDACIN ETZ	TOPICAL	KIT	N	F
clindamycin phos/skin clnsr 19	CLINDACIN PAC	TOPICAL	KIT	N	F
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	TOPICAL	GEL DAILY	N	F
clindamycin/benzoyl/emol cmb94	NEUAC	TOPICAL	CMB CR GEL	N	F
dapsone	DAPSONE	TOPICAL	GEL (GRAM)	N	F
dapsone	DAPSONE	TOPICAL	GEL W/PUMP	N	F
isotretinoin	ABSORICA	ORAL	CAPSULE	N	F
isotretinoin	ISOTRETINOIN	ORAL	CAPSULE	N	F
isotretinoin, micronized	ABSORICA LD	ORAL	CAPSULE	N	F
tazarotene	FABIOR	TOPICAL	FOAM	N	F
tazarotene	TAZAROTENE	TOPICAL	FOAM	N	F
tretinoin microspheres	TRETINOIN MICROSPHERE	TOPICAL	GEL W/PUMP	N	F
tretinoin/benzoyl peroxide	TWYNEO	TOPICAL	CREAM (G)	N	F
trifarotene	AKLIEF	TOPICAL	CREAM (G)	N	F
benzoyl peroxide	EPSOLAY	TOPICAL	CREAM (G)		F
salicylic acid	DERMACINRX ATRIX	TOPICAL	LIQUID		O

ROSACEA PRODUCTS

Generic	Brand	Route	Form	PDL
azelaic acid	AZELAIC ACID	TP	GEL (GRAM)	Y
brimonidine tartrate	BRIMONIDINE TARTRATE	TP	GEL W/PUMP	
benzoyl peroxide	EPSOLAY	TP	CREAM (G)	
azelaic acid	FINACEA	TP	GEL (GRAM)	Y
azelaic acid	FINACEA	TP	FOAM	N
ivermectin	IVERMECTIN	TP	CREAM (G)	N
metronidazole	METROCREAM	TP	CREAM (G)	
metronidazole	METROGEL	TP	GEL (GRAM)	
metronidazole	METRONIDAZOLE	TP	LOTION	
metronidazole	METRONIDAZOLE	TP	GEL (GRAM)	
metronidazole	METRONIDAZOLE	TP	CREAM (G)	
metronidazole	METRONIDAZOLE	TP	GEL (GRAM)	
metronidazole	METRONIDAZOLE	TP	GEL W/PUMP	N
brimonidine tartrate	MIRVASO	TP	GEL W/PUMP	
oxymetazoline HCl	RHOFADE	TP	CREAM (G)	
metronidazole	ROSADAN	TP	GEL (GRAM)	
metronidazole	ROSADAN	TP	CREAM (G)	
metronidazole/skin cleanser 23	ROSADAN	TP	KIT CL-CRM	
metronidazole/skin cleanser 23	ROSADAN	TP	KIT CL-GEL	
ivermectin	SOOLANTRA	TP	CREAM (G)	N

ORAL TETRACYCLINES

Generic	Brand	Route	Form	PDL
doxycycline hyclate	DOXYCYCLINE HYCLATE	ORAL	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	ORAL	CAPSULE	Y
doxycycline hyclate	ED DOXY-CAPS	ORAL	CAPSULE	Y
doxycycline hyclate	MORGIDOX	ORAL	CAPSULE	Y
tetracycline HCl	TETRACYCLINE HCL	ORAL	CAPSULE	Y
doxycycline hyclate	VIBRAMYCIN	ORAL	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	ORAL	SUSP RECON	Y
doxycycline hyclate	DOXYCYCLINE HYCLATE	ORAL	TABLET	Y
doxycycline hyclate	LYMEPAK	ORAL	TABLET	Y
doxycycline monohydrate	DOXYCYCLINE IR-DR	ORAL	CAP IR DR	N
doxycycline monohydrate	ORACEA	ORAL	CAP IR DR	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	ORAL	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL	ORAL	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL ER	ORAL	TAB ER 24H	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	ORAL	TABLET	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	ORAL	TABLET	N
minocycline HCl	MINOCYCLINE HCL	ORAL	TABLET	N
omadacycline tosylate	NUZYRA	ORAL	TABLET	N
doxycycline hyclate	DORYX	ORAL	TABLET DR	N
doxycycline hyclate	DORYX MPC	ORAL	TABLET DR	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	ORAL	TABLET DR	N
demeclocycline HCl	DEMECLOCYCLINE HCL	ORAL	TABLET	
tetracycline HCl	TETRACYCLINE HCL	ORAL	TABLET	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to January 14, 2026>

1	Rosacea/	3614
2	Acne Vulgaris/	14547
3	Acne Conglobata/	27
4	Acne Fulminans.mp.	226
5	1 or 2 or 3 or 4	17841
6	Adapalene/	473
7	Adapalene, Benzoyl Peroxide Drug Combination/	26
8	azelaic acid.mp. or Dicarboxylic Acids/	4794
9	Benzoyl Peroxide/	1250
10	exp Clindamycin/	6406
11	Metronidazole/	14440
12	Anti-Bacterial Agents/ or Erythromycin/	464232
13	Sulfacetamide/	356
14	10 or 11 or 12 or 13	476497
15	Administration, Topical/	42104
16	14 and 15	3317
17	Tretinoin/	24322
18	tazarotene.mp. or Retinoids/	7146
19	trifarotene.mp.	77
20	clascoterone.mp.	79
21	Brimonidine Tartrate/	1640
22	Ivermectin/	8397
23	Oxymetazoline/	725
24	6 or 7 or 8 or 9 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	50093
25	5 and 24	2462
26	limit 25 to (english language and humans and yr="2021 -Current")	300
27	limit 26 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or "systematic review")	43

Appendix 3: Key Inclusion Criteria

Population	Adults and children with acne conglobata, acne fulminans, severe acne vulgaris, or rosacea
Intervention	Acne: Topical acne therapies and oral tetracyclines (see **Appendix 1**) Rosacea: topical metronidazole, azelaic acid, ivermectin, brimonidine, and oxymetazoline and oral tetracyclines
Comparator	Placebo or active treatment
Outcomes	Lesion reduction, improved symptoms, adverse reactions
Timing	12 weeks
Setting	Outpatient Therapy

Acne and Rosacea Topical Medications

Goal(s):
- Ensure that medications for acne and rosacea are used appropriately for FDA-approved conditions for adults and children.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred drugs in the Acne and Rosacea medications class

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 an FDA-approved age and indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the diagnosis funded by OHP? HERC guideline notes 65 and 132 describe funding status based on disease severity: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-132.docx https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-GN-065.docx	**Yes:** Go to #6	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #5.

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 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 for at least 8 weeks? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.
7. Has a baseline assessment of acne or rosacea severity been documented using one of the following metrics: • Number of inflammatory lesions • Severity of acne or rosacea using Investigator's Global Assessment (IGA) as clear, almost clear, mild, moderate, or severe, or very severe or other assessment tool? • Patient's perception of quality of life using the Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), or other assessment tool?	**Yes:** Approve for up to 12 months Document baseline assessment: _____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for management of acne or rosacea?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
2. Have the patient's symptoms improved after using therapy as directed? • Reduction in inflammatory lesion count • At least 2-point improvement on the Investigators' Global Assessment score or a score of 0 (clear) or 1 (almost clear). • At least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from when treatment started. • Documented improvement using another assessment tool	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/26 (DM); 12/22; 02/21 (SF); 06/20; 11/18
Implementation: TBD; 1/1/23; 7/1/20; 1/1/1

Tetracyclines (Oral)-Quantity Limit

Goal(s):
- Restrict use of oral tetracyclines to OHP-funded diagnoses in adults. Allow case-by-case review for members covered under the EPSDT program.
- Prevent inappropriate use beyond two, 14-day supplies within a 3-month time period
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:
- Up to 12 months

Requires PA:
- Long-term use of oral tetracyclines beyond two, 14-day supplies in a 3-month timeframe

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 therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for an FDA-approved indication?	**Yes**: Go to #4	**No:** Pass to RPh. If clinic provides supporting literature: Go to #4 If not supported by literature: Deny; medical appropriateness
4. Is this an OHP-funded diagnosis?	**Yes**: Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #7~~6~~.
5. Is the requested agent a preferred product?	**Yes:** Approve for duration of prescription or up to 6 months, whichever is less.	**No:** Go to #6
6. 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 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.
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.

Approval Criteria		
8. 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:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.
9. Is the request for treatment of moderate to severe acne or rosacea?	**Yes:** Go to #10	**No:** Approve for duration of prescription or up to 6 months, whichever is less.
10. Has a baseline assessment of acne or rosacea severity been documented using one of the following metrics: • Number of inflammatory lesions • Severity of acne or rosacea using Investigator's Global Assessment (IGA) as clear, almost clear, mild, moderate, or severe, or very severe or other assessment tool? • Patient's perception of quality of life using the Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), or other assessment tool?	**Yes:** Approve for up to 12 weeks Document baseline assessment:_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for acne or rosacea?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
2. Have the patient's symptoms improved after using therapy as directed? • Reduction in inflammatory lesion count • At least 2-point improvement on the Investigators' Global Assessment score or a score of 0 (clear) or 1 (almost clear). • At least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from when treatment started. • Documented improvement using another assessment tool.	**Yes**: Approve for up to 12 weeks	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *4/26 DM); 12/22; 5/17 (MH)*
Implementation: *TBD; 1/1/23; 7/1/17*