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 7th, 2022 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. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	A. Gibler (OHA)
	F. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	B. Origer (Chair)
	A. Oncology Prior Authorization Updates	
	B. Orphan Drug Policy Updates	
	1. Public Comment	
	III. DUR NEW BUSINESS	
1:25 PM	A. Citizenship Waived Medical (CWM) Coverage Update	S. Servid (OSU)
	1. Coverage Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
1:40 PM	B. Prior Authorization Updates	S. Servid (OSU)
	1. Botulinum Toxins	
	2. Drugs for Non-funded Conditions	
	3. PDL Preferred/Non-preferred	
	4. Public Comment	
	5. Discussion and Clinical Recommendations to OHA	

IV. DUR OLD BUSINESS

1:55 PM	A. Hepatitis C Direct-Acting Antivirals Policy Discussion	A. Gibler (OHA)
	1. Policy Discussion	D. Weston (OHA)
	2. Prior Authorization Update	M. Herink (OSU)
	3. Public Comment	
	4. Discussion and Clinical Recommendations to OHA	

V. PREFERRED DRUG LIST NEW BUSINESS

2:25 PM	A. Sickle Cell Disease Literature Scan	K. Sentena (OSU)
	1. Literature Scan/Prior Authorization Update	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:40 PM	B. Fabry Disease Literature Scan	D. Moretz (OSU)
	1. Literature Scan/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
2:55 PM	BREAK	
3:10 PM	C. Voxzogo™ (vosoritide) New Drug Evaluation	D. Engen (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
3:25 PM	D. Vyvgart™ (efgartigimod alfa-fcab) New Drug Evaluation	K. Sentena (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
3:40 PM	E. Fluoroquinolone Class Update	D. Moretz (OSU)
	1. Class Update	
	2. Public Comment	
	3. Discussion and Clinical Recommendations to OHA	
4:00 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	

VIII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Dental3	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2024
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2024
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2024
Vacant	Physician			December 2024

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 3rd, 2022 1:00 - 5:00 PM

Via Zoom webinar

MEETING MINUTES

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

Members Present: Cat Livingston, MD; Stacy Ramirez, PharmD; Tim Langford, PharmD; Caryn Mickelson, PharmD; Robin Moody, MPH; Bill Origer, MD; Russ Huffman, PMHNP; Patrick DeMartino, MD; Eddie Saito, PharmD

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

Audience: Ashlee Waring, AstraZeneca; Becky Gonzales; Ben Dillon; Brandie Feger, Advanced Health; Camille Kerr; Carol Vuceta, Sanofi; China Izatt, Takeda Oncology; Jill Conner, Sanofi; Craig Sexton; Deb Profant; Jack Meloro, EveryLife Foundation for Rare Diseases; Jason Kniffin; John Breen, SOBI Account Director; John McDonald, Scynexis Dir Nat Accts; **Jordana Wollman, AstraZeneca***; Kendra Davies; Laura Jeffcoat, AbbVie; **Heidi Kresken, Scynexis***; Lee Stout, Chiesi USA; Madeline Shurtleff; Matt Worthy, OHSU; Melissa Roy, Otsuka; Melissa Walker, Arinia Pharmaceuticals; Michael Foster, BMS; Michele Sabados, Alkermes; Michelle Plotner, AstraZeneca; Mike Donabedian, Sarepta Therapeutics; Nana Ama Kuffour, IHN; **Nicole Slawny, Aurinia Pharmaceuticals***; Olaf Reinwald, GBT; Paul Thompson, Alkermes; **Raffaella Colzani, Sanofi Genzyme***; Roy Lindfield, Sunovion; Saghi Maleki; Takeda Pharmaceuticals; Dennis Schaffner, Sanofi; Sean Staff; ChemoCentryx; Sophia Yun, Janssen; Steve Angelcyk, BD Diabetes; Tiina Andrews, UHA; Stefanie Uhrich; YJ Shukla, MODA Health

(*) Provided verbal testimony
Written testimony: Posted to OSU Website

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I. CALL TO ORDER

A. Roll Call & Introductions
- Called to order at approx. 1:02 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 again serve as Chair and Dr. Origer as Vice-Chair
ACTION: Motion to approve, 2nd, all in favor

D. Approval of Agenda and December 2021 Minutes presented by Roger Citron
ACTION: Motion to approve, 2nd, Dr. Saito abstained and everyone else in favor

E. Department Update provided by Andrew Gibler, PharmD

F. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. **P&T Annual Report**

B. **P&T Operating Procedures**

C. **P&T Methods**

D. **Parenteral Antipsychotics Literature Scan**
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

E. **Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS) Literature Scan**
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

F. **Oncology Prior Authorization (PA) Updates**
Recommendations:
- Add: Besremi® (ropeginterferon alfa-2b-njft); and Fyarro™ (sirolimus albumin-bound nanoparticles) to Table 1 in the Oncology Agents prior authorization (PA) criteria
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. **Quarterly Utilization Report:** Roger Citron, RPh

B. **ProDUR Report**: Lan Starkweather, PharmD

C. **RetroDUR Report**: Dave Engen, PharmD

D. **Oregon State Drug Review**: Kathy Sentena, PharmD
- **Therapeutic Uses for Cannabinoids**
- **Updates in Heart failure Therapy: New Drugs and Indications**

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IV. DUR NEW BUSINESS

A. **Respiratory Syncytial Virus (RSV) Literature Scan and Policy Update:**
Kathy Sentena, PharmD
Recommendation:
- Update the RSV PA criteria to correlate with state guidance on season onset
ACTION: Motion to approve, 2nd, all in favor

V. PREFERRED DRUG LIST NEW BUSINESS

A. **Oral Antifungals Class Update with New Drug Evaluation (NDE)**:
Kathy Sentena, PharmD
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Maintain Brexafemme® (ibrexafungerp) as non-preferred on the PDL
- Evaluate costs in executive session
Public Comment: Heidi Kresken, Scynexis
ACTION: Motion to approve, 2nd, all in favor

B. **Pompe Disease Class Update with NDE**: Dave Engen, PharmD
Recommendations:
- Add Nexviazyme™ (avalglucosidase alfa) to the Lysosomal Storage Disorders class and designate as non-preferred
- Update the PA criteria for Pompe Disease drugs to include avalglucosidase alfa
- Evaluate costs in executive session
Public Comment: Raffaella Colzani, Sanofi Genzyme
ACTION: The Committee recommended amending the proposed criteria so that question #5 asks for provider assessment of risk factors for adverse events and so that question #14 asks whether baseline tests have been performed
Motion to approve, 2nd, all in favor

C. **Immunosuppressant Class Update with NDEs:** Sara Fletcher, PharmD
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Move Saphnelo™ (anifrolumab-fnia) into the TIMS class
- Update belimumab PA criteria
- Implement PA for voclosporin to ensure appropriate use
- Implement PA for anifrolumab-fnia with proposed edits
- Evaluate costs in executive session

Public Comment: Jordana Wollman, AstraZeneca; Nicole Slawny, Aurinia Pharmaceuticals
ACTION: Motion to approve, 2nd, all in favor

E. **Oral Glucocorticoids Class Review**: Deanna Moretz, PharmD
Recommendations:
- Add the Oral Glucocorticoids class to the PDL
- Add at least one oral formulation of each glucocorticoid to the PDL after review of costs in the executive session
ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Cat Livingston, MD; Stacy Ramirez, PharmD; Tim Langford, PharmD; Caryn Mickelson, PharmD; Bill Origer, MD; Russ Huffman, PMHNP; Patrick DeMartino, MD; Eddie Saito, PharmD

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

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Parenteral Antipsychotics Literature Scan**
Recommendation: Make Invega Hafyera preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **Inhibitors of the RAAS Literature Scan**
Recommendation: Make fosinopril, quinapril, candesartan preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

C. **Oral Antifungals Class Update and NDE:**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

D. **Pompe Disease Class Update and NDE**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

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E. **Oral Glucocorticoids Class Review**
Recommendation: Make the following agents non-preferred on the PDL: Hemady®; Alkindi® Sprinkle; Pediapred®; Millipred™; prednisolone sodium phosphate solution; and prednisolone sodium phosphate disintegrating tablets. The Committee recommended making all other currently available oral formulations preferred on the PDL. New oral glucocorticoid formulations will be designated non-preferred until reviewed by the Committee
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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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
tebentafusp-tebn	KIMMTRAK

Recommendation:

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

Oncology Agents

Goal(s):

To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #6
6. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #8
8. 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 #9	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
9. 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 3/9/2022)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG

Generic Name	Brand Name
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ

Generic Name	Brand Name
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
mobecertinib	EXKIVITY
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA

Generic Name	Brand Name
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
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

Generic Name	Brand Name
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRACK
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
Sutimlimab-jome	ENJAYMO

Recommendation:

- PA was modified to include new, recently approved orphan drugs.

Orphan Drugs

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

Length of Authorization:
- Up to 6 months

Requires PA:
- See Table 1 (pharmacy and physician administered claims)

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

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Avacopan (TAVNEOS)	Severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with glucocorticoids.	≥18 yrs	30 mg (three 10 mg capsules) twice daily, with food	Baseline Monitoring • Liver function tests ALT, AST, ALP, and total bilirubin • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 wks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 mo TIO ≥ 2 yrs	Pediatric <18 yrs: Initial (administered SC every 2 wks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult:	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D

			XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	(cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks) Initial: 0.4mg/kg Month 1: 0.7 mg/kg	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

			Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months **≥ 20 kg** Loading: 3 mg/kg once/month for 3 doses	N/A

			Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg ~~subcutaneously~~SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 1 yr	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 390 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K

Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given ~~intravenously~~ IV every 2 to 4 days	Baseline Monitoring • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) Ongoing Monitoring • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg** 6500 mg **≥75 kg** 7500 mg	Baseline Monitoring • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup), *Streptococcus pneumonia*, and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenously; mo = months; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years				

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	**Yes:** Approve for up to 6 months Document benefit	**No:** Pass to RPh. Deny; medical appropriateness

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

P&T/DUR Review: 4/22 (SF); 12/21 ~~(SF)~~; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: TBD; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

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Prior Authorization Criteria Update: Emergency Drug Coverage for Citizenship Waived Medical (CWM)

Purpose of Update:

Non-citizens who also meet standard definitions for Medicaid eligibility are eligible for emergency treatment and can be covered by the state under the Citizenship Waived Medical (CWM) benefit. Coverage is limited to diagnoses for which the absence of treatment could result in serious jeopardy to the health of the patient (or an unborn child), serious impairment to bodily functions, or serious dysfunction of any bodily organ or part.[1] Currently, this benefit includes drug coverage for cancer, end stage renal disease for patients on dialysis, and drug therapy to support kidney transplants. The Oregon Health Authority is currently evaluating other conditions and diagnoses which may be eligible for coverage. To ensure prescription drug use is limited to covered conditions, implementation of the following PA criteria is recommended for the CWM benefit plan. Clinical criteria ensuring medical appropriateness and medical necessity will also still apply.

Recommendation:

- Implement prior authorization criteria for drugs prescribed for patients with the CWM benefit.
- If emergency drug coverage is expanded to other conditions in future, update PA criteria with relevant diagnoses as appropriate.

References:

1. Oregon Administrative Rules. Chapter 410 Division 120 (OAR 410-120-1210): Medical Assistance Benefit Packages and Delivery System. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=286645. Accessed March 8, 2022.

Emergency Drug Coverage for Citizenship Waived Medical (CWM)

Goal(s):

- Restrict use for conditions when lack of therapy will result in serious jeopardy to the health of the patient or an unborn child, serious impairment to bodily functions, or serious dysfunction of any bodily organ or part

Length of Authorization:

Up to 12 months (criteria specific)

Requires PA:

- All drugs for the CWM benefit

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 treatment related to any of the diagnoses in Table 1 for which the absence of treatment could result in: • Serious jeopardy to the patient's health • Serious impairment to bodily functions OR • Serious dysfunction of any bodily organ or part?	**Yes**: Go to #3	**No:** Go to #4
3. Is there documentation that the request is for primary or secondary preventative therapy? Note: chemoprophylaxis for primary prevention (to reduce risk of the diagnosis) and secondary prevention (to prevent disease recurrence after complete remission) are not covered.	**Yes:** Pass to RPh. Deny; not covered for CWM benefit Preventative therapy is not covered.	**No:** Adjudicate per clinical criteria (if pertinent). In the absence of specific clinical criteria, therapy can be approved for up to 12 months.

Approval Criteria		
4. Is treatment for a covered ancillary diagnosis in Table 2?	**Yes:** Adjudicate per clinical criteria (if pertinent). In the absence of specific clinical criteria, therapy can be approved for up to 12 months.	**No:** Pass to RPh. Go to #5.
5. RPh only: Provider should include documentation that ancillary diagnoses are 1) related to a covered condition and 2) drug therapy for the ancillary diagnosis is necessary to treat the covered condition. RPh can use clinical judgement to adjudicate requests per clinical criteria or deny based on the documentation provided. If ancillary diagnoses are provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Table 1. Conditions covered for CWM

ICD-10	Condition
C00x-C96x	Malignant neoplasms
D00x-D49x	Neoplasms
N18.6	End stage renal disease (on dialysis)
T86.1-T86.9; Z94.0	Kidney transplant

Table 2. Common covered ancillary conditions

Condition (ICD-10 when a specific code is available)
Agranulocytosis secondary to cancer chemotherapy (D70.1) Antineoplastic chemotherapy induced pancytopenia (D61.810) Febrile neutropenia
Blood-clots secondary to cancer or venous access necessary for cancer treatment
Cancer-related pain
Chemotherapy-induced nausea and vomiting
Tumor lysis syndrome (E88.3)

P&T/DUR Review: 4/22 (SS)
Implementation: 1/1/22

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Prior Authorization Criteria Update: Botulinum Toxins

Purpose of Update:

To provide clarification to existing prior authorization (PA), specifically for use in overactive bladder refractory or intolerant to anticholinergic medications.

Recommendation:

- Update PA per Appendix 1.

Botulinum Toxins

Goal(s):

- Approve use of botulinum toxins for conditions funded under the Oregon Health Plan (OHP) and~~conditions~~ supported by evidence of benefit.
- Require positive response to therapy for continued use to manage~~in~~ chronic migraine headaches or overactive bladder.

Length of Authorization:

- From 90 days to 12 months

Requires PA:

- Use of botulinum toxins (billed as a physician administered or pharmacy claim) without associated dystonia or neurological disease diagnosis in last 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/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor muscle over-activity (~~e.g.,~~ "~~-~~overactive bladder")?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83) b. Strabismus due to a neurological disorder (H50.89) c. Blepharospasm (G24.5) d. Spasmodic torticollis (G24.3) e. Torsion dystonia (G24.9) f. Achalasia (K22.0)	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
4. Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #8
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient had an ~~in~~adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs~~pharmacological prophylaxis therapies~~? • Propranolol immediate-release, metoprolol, or atenolol~~Beta-blockers~~ • Topiramate, valproic acid, or divalproex sodium • ~~Tricyclic antidepressants~~Amitriptyline, nortriptyline, or venlafaxine • ~~Anticonvulsants~~	**Yes:** Go to #7 Baseline headaches/month: _____.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve no more than 2 injections given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).
8. Is botulinum toxin treatment ~~for idiopathic or neurogenic~~ detrusor muscle over-activity ("overactive bladder")~~(ICD10-CM N32.81)~~?	**Yes:** Go to #9	**No:** Pass to RPh. Go to #10

Approval Criteria		
9. Has the patient had an inadequate response to, or is intolerant of, ≥2 of the following ~~incontinence anti-muscarinic~~ drugs? ~~(e.g., fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?~~ a. Fesoterodine (OHP preferred) b. Oxybutynin (OHP preferred) c. Solifenacin (OHP preferred) d. Darifenacin e. Flavoxate f. Mirabegron g. Tolterodine h. Trospium ~~a.~~i. Vibegron	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

9.10. RPh only: Review treating condition and ICD-10 code. ICD-10 codes included in the tables below are denied. If ICD-10 code is not included in the tables below, mMedical literature with evidence for use in funded conditions must be submitted by the prescriber. RPh may approve for up to 12 months for funded conditions with evidence of benefitand determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
▪ Axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) ▪ Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259) ▪ Facial nerve disorders (G510-G519) ▪ Spastic dysphonia (J387) ▪ Anal fissure (K602) ▪ Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61) ▪ Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788) ▪ Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549) ▪ Disorders of soft tissue (M5410; M609; M790-M792; M797) ▪ Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51) ▪ Gastroparesis (K3184) ▪ Lateral epicondylitis (tennis elbow)) (M7710-M7712)
Deny for medical appropriateness because evidence of benefit is insufficient

- Dysphagia (R130; R1310-R1319)
- Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26)
- Other disorders of binocular eye movements (e.g., esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518)
- Tics (F950-F952; F959)
- Laryngeal spasm (J385)
- Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413)
- Spasm of muscle in absence of neurological diagnoses (M6240-M62838)
- Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838)
- Amyotrophic sclerosis (G1221)
- Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417)
- Essential tremor (G25.0)
- Hemifacial spasm (G513)
- Occupational dystonias (e.g., “Writer’s cramp”) (G248, G249)
- Hyperplasia of the prostate (N400-403; N4283)
- Conditions of the back and spine for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions. See Guideline Note 37.

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a reduction of ≥7 migraine headache days per month compared to baseline migraine headache frequency?	**Yes:** Approve no more than 2 injections given ≥3 months apart. Baseline:____ migraine headaches/month Current:____ migraine headaches/month	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of ~~idiopathic or neurogenic~~ detrusor muscle over-activity ("overactive bladder")?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months • Baseline:____ urine frequency/day • Current:____ urine frequency/day -or- • Baseline:____ urine incontinence episodes/day • Current:____ urine incontinence episodes/day	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *4/22 (AG); 5/19 (KS); 9/18; 5/18; 11/15; 9/14; 7/14*
Implementation: *TBD; 11/1/2018; 7/1/18; 10/13/16; 1/1/16*

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Prior Authorization Criteria Update: Non-Preferred Drugs in Select PDL classes and Drugs for Non-Funded Conditions

Purpose of Update:

To align prior authorization (PA) criteria with Oregon Health Authority Statement of Intent 4 (SOI4), which addresses role of the prioritized list for conditions in patients aged 21 year of age or younger if treatment has or is expected to improve the patient's ability to grow, develop or participate in school.[1]

Recommendation:

- Update prior authorization criteria for Non-Preferred Drugs in Select PDL Classes and Drugs for Non-Funded Conditions to align with final version of SOI4.

References:

1. *Statement of intent 4,* Available at: https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-SOI-004.docx Accessed: March 2, 2022.

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

Goal(s):

- Ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

- Up to 6 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**No**: Go to #5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less. • If not funded and patient is over 21 years of age: Deny; not funded by the OHP. • If not funded and patient is 21 year of age or younger: Approve for 6 months, or for length of the prescription, whichever is less if treatment has or is expected to improve the patient's ability to grow, develop or participate in school.[1] If no documentation is provided: Deny; not funded by the OHP.		

1. *Statement of intent 4:* https://www.oregon.gov/oha/HPA/DSI-HERC/SearchablePLdocuments//Prioritized-List-SOI-004.docx

P&T / DUR Review: *4/22 (SS); 7/15 (RC), 9/10; 9/09; 5/09*
Implementation: *TBD; 10/13/16; 8/25/15; 8/15; 1/1/11, 9/16/10*

Drugs for Non-funded Conditions

Goal:

- Restrict use of drugs reviewed by the Oregon Pharmacy & Therapeutics (P&T) Committee without evidence for use in Oregon Health Plan (OHP)-funded conditions.

Length of Authorization:

- Up to 6 months.

Requires PA:

- A drug restricted by the P&T Committee due to lack of evidence for conditions funded by the OHP.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Go to #3
3. Is the patient 21 years of age or younger AND is there documentation that the therapy is expected to improve the patient's ability to grow, develop or participate in school?	**Yes:** Approve for 6 months, or for length of the prescription, whichever is less	**No:** Deny; not funded by the OHP.
4. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

P&T / DUR Review: *4/22 (SS); 11/15 (AG)*
Implementation *TBD; 1/1/16*

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Prior Authorization Criteria Update: Direct Acting Antivirals for Hepatitis C Virus

Purpose of Update:

The purpose of this prior authorization (PA) update is to remove PA criteria for preferred hepatitis C medications for treatment naïve individuals.

There is high quality evidence that direct acting antiviral (DAA) regimens result in pooled sustained virologic response (SVR) rates of 95.5% to 98.9% across genotypes in the treatment of chronic hepatitis C virus (HCV) and have low rates of serious adverse events (1.9%; relative risk [RR] 1.90; 95% confidence interval [CI] 0.73 to 4.95) and withdrawals due to adverse events (0.4%).[1] There is also low quality evidence that SVR is associated with a decreased risk of all-cause mortality (hazard ratio [HR] 0.40; 95% CI 0.28 to 0.56, I^2 52.1%), liver-related mortality (HR 0.11; 95% CI 0.04 to 0.27), cirrhosis (HR 0.36; 95% CI 0.33 to 0.4) and hepatocellular carcinoma (HR 0.29; 95% CI 0.23 to 0.38) after adjustment for potential confounders.[1] Current guidelines from the Veterans Affairs[2], American Association for the Study of Liver Diseases, the Infectious Diseases Society of America[3] and European Association for the Study of the Liver[4] recommend that treatment with DAAs be offered to all patients with recently acquired (acute) or chronic HCV without delay.

The Oregon Drug Use Review/Pharmacy & Therapeutics Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options became available, real-world experience increased, and the community standard evolved, the P&T Committee has expanded treatment in a stepwise fashion to patients with less severe disease. Since March 2019, Oregon Health Authority (OHA) drug policy approves treatment for patients with chronic HCV regardless of disease severity, level of fibrosis or history of substance use disorder, but also ensures appropriate baseline laboratory screening (hepatitis B virus status, noninvasive screening for cirrhosis and history of previous HCV treatment).

In 2016, the World Health Organization released a proposal to eliminate hepatitis C as a public health threat by 2030. Consistent with this, the OHA includes health equity as a core value and is committed to eliminate health inequities by 2030. Most state Medicaid programs have similarly removed prior authorization (PA) criteria requiring fibrosis, sobriety and prescriber restrictions.[5] Additionally, at least 10 states have removed PA for uncomplicated patients entirely.[5] A previous hepatitis C policy evaluation found that overall utilization of DAAs in the Oregon Health Plan increased over time. Changes to the PA criteria in 2018 (expanded treatment to fibrosis stage 2) and 2019 (removed fibrosis and sobriety requirements) also resulted in an immediate increase in DAA utilization followed by stabilization and an increasing number of primary care prescribers.

Recommendation:

- Remove PA criteria and required case management for preferred DAA regimens for treatment-naïve patients with hepatitis C virus (**Appendix 1**). Continue to require PA for: retreatment of HCV; non-preferred DAAs; and for uses not FDA approved.
- Make sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) non-preferred and continue to reserve it for treatment-experienced individuals.

References:

1. Chou R, Dana T, Fu R, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. *Screening for Hepatitis C Virus Infection in Adolescents and Adults: A Systematic Review Update for the US Preventive Services Task Force*. Agency for Healthcare Research and Quality (US); 2020.
2. Department of Veterans Affairs HIV, Hepatitis, and Related Conditions Program. Chronic Hepatitis C Virus Infection: Treatment Considerations. March 2021. Available at: https://www.hepatitis.va.gov/pdf/Treatment-Considerations-2021-03-18-508.pdf.
3. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV Guidance: Recommendations for testing, managing and treating hepatitis C. January 2021. Available at: www.hcvguidelines.org.
4. EASL recommendations on treatment of hepatitis C: Final update of the series(☆). *Journal of hepatology*. Nov 2020;73(5):1170-1218. doi:10.1016/j.jhep.2020.08.018
5. The Center for Health Law and Policy Innovation of Harvard Law School (CHLPI) and the National Viral Hepatitis Roundtable (NVHR) Hepatitis C: The State of Medicaid Access 2022 Progress Report. Available at: https://stateofhepc.org/report/. Accessed: February 1, 2022.

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across hepatitis C treatments.
- Ensure appropriate patient regimen based on prior treatment experience and genotype.

Length of Authorization:

- 8-24 weeks

Requires PA:

- Non-preferred direct acting antivirals (DAAs)
- Preferred regimens for patients with treatment experience with a DAA

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of Hepatitis C infection?	**Yes:** Go to #3 Document baseline quantitative HCV RNA level _____	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Has <u>all</u> the following pre-treatment testing been documented: a. Genotype testing in past 3 years is required if the patient has decompensated cirrhosis, <u>prior treatment experience</u> with a DAA regimen, and if prescribed a regimen which is not pan-genotypic b. History of previous HCV treatment, viral load after treatment, and outcome are required only if there is documentation of treatment experience	**Yes:** Record results of each test and go to #4	**No**: Pass to RPh. Request updated testing.
4. Which regimen is requested?	Document and go to #5	
5. Has the patient been treated with a direct acting antiviral regimen previously?	**Yes:** Go to #6	**No:** Go to #8
6. Did the patient achieve a sustained virological response (SVR) at week 12 or longer following the completion of their last DAA regimen?	**Yes:** Go to #7	**No:** Document as treatment failure and treat as indicated for treatment experienced. Go to #8
7. Is this likely a reinfection, indicated by at least one of the following: a. Does the patient have ongoing risk factors for hepatitis C reinfection (e.g. sexually active men who have sex with men, persons who inject drugs), OR b. Is the hepatitis C infection a different genotype than previous	**Yes:** Document as reinfection. Use regimens recommended for treatment naïve patients. Go to #8	**No:** Document as treatment failure and treat as indicated for treatment experienced. Go to #8

Approval Criteria		
8. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Ledipasvir/sofosbuvir for GT 1a treatment-experienced infection; or c) Sofosbuvir/velpatasvir for GT 3 in cirrhosis or treatment-experienced infection	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #10? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #10 Document test and result.
10. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, age, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1 and Table 2**)? Note: Safety and efficacy of DAAs for children < 3 years of age have not been established Pediatric dosing available in **Table 3** and **Table 4**	**Yes:** Approve for 8-24 weeks based on duration of treatment indicated for approved regimen Referral will be made for optional case management (patient may choose to opt-in).	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Adults, and Adolescents 12 years of age and older with Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Treatment Naïve (Genotype 1-6)		
Treatment naïve, confirmed reinfection or prior treatment with PEGylated interferon/ribavirin	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	G/P x 8 weeks SOF/VEL x 12 weeks (baseline resistance testing recommended for GT3)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks SOF/VEL x 24 weeks (if ribavirin ineligible*)

Treatment Experienced (Genotype 1-6)		
Sofosbuvir based regimen treatment failures, including: Sofosbuvir + ribavirin Ledipasvir/sofosbuvir Velpatasvir/sofosbuvir	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x12 weeks G/P x 16 weeks (except GT3)
Elbasvir/grazoprevir treatment failures	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
Glecaprevir/pibrentasvir treatment failures	Non-cirrhotic or compensated cirrhosis	G/P + SOF + RBV x 16 weeks SOF/VEL/VOX x 12 weeks (plus RBV if compensated cirrhosis)
Multiple DAA Treatment Failures, including: sofosbuvir/velpatasvir/voxilaprevir glecaprevir/pibrentasvir + sofosbuvir	Non-cirrhotic or compensated cirrhosis	G/P + SOF + RBV x 16-24 weeks SOF/VEL/VOX x 24 weeks
Abbreviations: DAA = direct acting antiviral; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir and pibrentasvir; PEG = pegylated interferon; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir * Ribavirin ineligible/intolerance may include: 1) neutrophils < 750 mm^3, 2) hemoglobin < 10 g/dl, 3) platelets <50,000 cells/mm^3, autoimmune hepatitis or other autoimmune condition, hypersensitivity or allergy to ribavirin		
^ Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.		
Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin containing regimen is chosen is required.		
All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C).		
There is limited data supporting DAA regimens in treatment- experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.		
Definitions of Treatment Candidates • Treatment-naïve: Patients without prior HCV treatment. • Treat as treatment-naïve: Patients who discontinued HCV DAA therapy within 4 weeks of initiation or have confirmed reinfection after achieving SVR following HCV treatment. • Treatment-experienced: Patients who received more than 4 weeks of HCV DAA therapy.		

Table 2: Recommended Treatment Regimens for children ages 3 - 12 years of age with Hepatitis C virus.

Treatment History	Cirrhosis Status	Recommended Regimen
Treatment Naïve Genotype 1-6		
Treatment naïve, confirmed reinfection or prior treatment with pegylated interferon/ribavirin	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks

Treatment Experienced with DAA regimen
Note: Efficacy and safety extremely limited in treatment experienced to other DAAs in this population. Can consider recommended treatment regimens in adults if FDA approved for pediatric use. Recommend consulting with hepatologist.
Abbreviations: DAA = direct acting antiviral; G/P = glecaprevir and pibrentasvir; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir • All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C). • There is limited data supporting DAA regimens in treatment- experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.

Table 3: Recommended dosage of sofosbuvir/velpatasvir in pediatric patients 3 years of age and older:

Body weight	Dosing of sofosbuvir/velpatasvir
Less than 17 kg	One 150 mg/37.5 mg pellet packet once daily
17 kg to less than 30 kg	One 200 mg50 mg pellet packet OR tablet once daily
At least 30 kg	Two 200 mg/50 mg pellet packets once daily OR one 400 mg/100 mg tablet once daily

Table 4: Recommended dosage of glecaprevir/pibrentasvir in pediatric patients 3 years of age and older:

Body weight	Dosing of sofosbuvir/velpatasvir
Less than 20 kg	Three 50mg/20 mg pellet packets once daily
20 kg to less than 30 kg	Four 50 mg/20 mg pellet packets once daily
30 kg to less than 45 kg	Five 50 mg/20 mg pellet packets once daily
45 kg and greater **OR** **12 years of age and older**	Three 100mg/40 mg tablets once daily

P&T Review: *2/22 (MH); 10/21; 6/20; 9/19; 1/19; 11/18; 9/18; 1/18; 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *7/1/20; 1/1/20; 3/1/2019; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15*

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Drug Class Literature Scan: Drugs for Sickle Cell Disease

Date of Review: April 2022

Date of Last Review: June 2020
Literature Search: 05/01/20 – 12/23/21

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

Conclusions:
- One new clinical practice guideline and an expanded indication for voxelotor was identified in this drug class literature scan.
- Guidance from the National Institute for Health and Care Excellence (NICE) recommends crizanlizumab for use in patients with sickle cell disease (SCD) who are 16 years or older for prevention of recurrent vaso-occlusive crises (VOCs) (history of 2 or more) in the previous 12 months.[1]
- Voxelotor received an expanded indication for the treatment of SCD in pediatric patients 4 years of age and older.[2] One small, single-arm, open-label trial demonstrated that 36% of patients 4 years of age to less than 12 years of age treated with voxelotor experienced an increase in hemoglobin [Hb] of 1 g/dL or greater from baseline to week 24 (95% confidence interval [CI], 21.6% to 49.5%).[2]
- The hydroxyurea formulation, Siklos, was approved for the expanded indication for use in adult patients for the reduction in the frequency of painful crises and need for blood transfusions in patients with SCD with recurrent moderate to severe painful crises. Approval was based on observational, cohort data with small changes in efficacy outcomes.[3]
- The Food and Drug Administration (FDA) updated safety warnings and precautions for 2 drugs in the SCD drug class. Hemolytic anemia is associated with patients who use hydroxyurea and long-term use of hydroxyurea has demonstrated a risk of secondary leukemia.[4] Crizanlizumab prescribing information was updated with a risk of infusion-related reactions that may be severe and require hospitalization.[5]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on the evidence review.
- Update prior authorization (PA) criteria to include the expanded age indication for voxelotor.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The SCD drug class was last reviewed in June 2020.
- Hydroxyurea capsules (generic formulation only) were added as a preferred treatment and voxelotor and crizanlizumab were designated as non-preferred. L-glutamine maintained non-preferred status and the PA was amended to include l-glutamine products.

Author: Kathy Sentena, PharmD

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. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

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

After review, 8 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). [6–13]

New Guidelines:

NICE – Crizanlizumab for Preventing Sickle Cell Crises in Sickle Cell Disease
New guidance from NICE on the use of crizanlizumab for SCD was published 2021.[1] Evaluation of the evidence was based on the SUSTAIN[14] trial which found that crizanlizumab may reduce the number of sickle cell crises compared to supportive care, with or without hydroxyurea. NICE found insufficient evidence on the long-term benefits of crizanlizumab. NICE requires requests for crizanlizumab be reviewed by specialists and according to labeling.

Recommendations for use of crizanlizumab:
- An option for preventing recurrent VOC in patients 16 years of age or older with SCD.[1]
- Patients will be eligible who meet the following criteria:
    - Confirmed diagnosis of SCD
    - Age of 16 years or older with a history of 2 or more VOCs in the previous 12 months

New Indications:
Voxelotor (Oxbryta): In December 2021, voxelotor received an expanded indication for the use in pediatric patients 4 years of age and older.[2] The indication was based off data from patients with SCD ages 4 to less than 12 years in a small (n=45) open-label, , single arm, phase 2 trial. There were an additional 11 patients who were aged 12 to less than 17 years. Inclusion criteria required patients to have a baseline Hb of less than or equal to 10.5 g/dL. The HbSS or HbS/beta^0-thalassemia genotype was present in every patient. The dose of voxelotor was based on weight and given as 600 mg, 900 mg, or 1,500 mg once daily for patients weighing 10 kg to less than 20 kg, 20 kg to less than 40 kg, or 40 kg or greater, respectively.[2] Doses were provided as tablets to be used in an oral suspension. Voxelotor doses of 1,500 mg day were given to patients 12 to less than 17 years of age. Stable doses of hydroxyurea were allowed as background therapy and

utilized by 80% of participants. The trial demonstrated that 36% of patients 4 years of age to less than 12 years of age treated with voxelotor experienced an increase in hemoglobin [Hb] of 1 g/dL or greater from baseline to week 24 (95% confidence interval [CI], 21.6% to 49.5%).[2]

Hydroxyurea (Siklos): Hydroxyurea received an expanded indication in December 2021 for the use in adult patients to reduce the frequency of painful crises and to reduce the need for blood transfusions in those with sickle cell anemia with recurrent moderate to severe painful crises.[15] Approval was based off of one, observational, phase IV, cohort study in 1906 adult participants. Changes in vaso-occlusive crises last >48 hours, acute chest syndrome episodes, hospitalizations and the percentage of patients requiring blood transfusions within three first 12 months were compared to the previous 12 months. In comparison to 12 months prior, vaso-occlusive crises were reduced by 0.9 episodes ($p<0.05$), acute syndromes by 0.2 ($p<0.05$), hospitalizations by 0.6 ($p<0.05$), number of days of hospitalizations for SCD by 3.7 days ($P<0.05$) and number of patients with at least one blood transfusion by 223 patients ($p<0.001$).[3] Neutropenia (4%) and thrombocytopenia (5%) were the most common adverse reactions.[3]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Hydroxyurea[4,15]	Droxia / Siklos	July 2021	Warnings and precautions	Hemolytic anemia has been reported in patients taking hydroxyurea. Acute jaundice or hematuria in the presence of worsening anemia may be indicative of hemolysis and patients should be evaluated. Hydroxyurea should be discontinued if confirmed diagnosis of hemolytic anemia is made.
Hydroxyurea[4]	Droxia	February 2021	Warnings and Precautions	Secondary leukemia has been reported with long-term use of hydroxyurea in patients with sickle cell disease. Patients who use hydroxyurea on a long-term basis should have regular blood counts performed to monitor for leukemia.
Crizanlizumab[5]	Adakveo	July 2021	Warnings and precautions	Infusion-related reactions, including severe pain and potentially hospitalization have been reported. Monitor patients for infusion-related reactions (e.g., headache, pain in various locations, fever, chills, nausea, vomiting, diarrhea, fatigue, dizziness, pruritus, uticaria, sweating, shortness of breath or wheezing) and discontinue if reactions are severe.

References:

1. National Institute for Health and Care Excellence. Crizanlizumab for Preventing Sickle Cell Crises in Sickle Cell Disease. Technology Appraisal Guidance. November 2021.

2. Oxbryta (voxelotor) [product information]. Global Blood Therapeutics, Inc., South San Franscisco, CA. November 2019.

3. de Montalembert M, Voskaridou E, Oevermann L, et al. Real-Life Experience with Hydroxyurea in Patients with Sickle Cell Disease: Results from the Prospective ESCORT-HU Cohort Study. *Am J Hematol*. 2021;96(10):1223-1231. doi:10.1002/ajh.26286

4. Droxia (hydroxyurea) [product information]. Princeton, NJ: Bristol-Myers Squibb Company. July 2021.

5. Adakveo (crizanlizumab-tmca) [product Information]. Novartis Pharamaceuticals Corporation, East Hanover, NJ. November 2019.

6. Wadman RI, Pol WL van der, Bosboom WM, et al. Drug Treatment for Spinal Muscular Atrophy Types II and III. *Cochrane Database of Systematic Reviews*. 2020;(1). doi:10.1002/14651858.CD006282.pub5

7. Estcourt LJ, Kimber C, Hopewell S, Trivella M, Doree C, Abboud MR. Interventions for Preventing Silent Cerebral Infarcts in People with Sickle Cell Disease. *Cochrane Database of Systematic Reviews*. 2020;(4). doi:10.1002/14651858.cd012389.pub3

8. Thom H, Jansen J, Shafrin J, et al. Crizanlizumab and Comparators for Adults with Sickle Cell Disease: a Systematic Review and Network Meta-analysis. *BMJ Open*. 2020;10(9):e034147. doi:10.1136/bmjopen-2019-034147

9. Ryan N, Dike L, Ojo T, et al. Implementation of the Therapeutic use of Hydroxyurea for Sickle Cell Disease Management in Resource-constrained Settings: a Systematic Review of Adoption, Cost and Acceptability. *BMJ Open*. 2020;10(11):e038685. doi:10.1136/bmjopen-2020-038685

10. Shih S, Cohen LL. A Systematic Review of Medication Adherence Interventions in Pediatric Sickle Cell Disease. *Journal of Pediatric Psychology*. 2020;45(6):593-606. doi:10.1093/jpepsy/jsaa031

11. Hasson C, Veling L, Rico J, Mhaskar R. The Role of Hydroxyurea to Prevent silent Stroke in Sickle Cell Disease: Systematic Review and Meta-analysis. *Medicine*. 2019;98(51):e18225. doi:10.1097/MD.0000000000018225

12. Cieri-Hutcherson NE, Hutcherson TC, Conway-Habes EE, et al. Systematic Review of l-glutamine for Prevention of Vaso-occlusive Pain Crisis in Patients with Sickle Cell Disease. *Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy*. 2019;39(11):1095-1104. doi:10.1002/phar.2329

13. Tanriverdi LH, Sarici A, Erkurt MA, Parlakpinar H. The Efficacy of Voxelotor, 900 mg in patients with Sickle Cell Anaemia: A Meta-analysis of the Randomised Controlled Trials. *Int J Clin Pract*. 2021;75(6):e13967. doi:10.1111/ijcp.13967

14. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *New England Journal of Medicine*. 2017;376(5):429-439. doi:10.1056/NEJMoa1611770

15. Siklos (hydroxyurea) [product information]. Bryn Mawr, PA: Medunik USA. December 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
hydroxyurea	HYDREA	CAPSULE	Y
hydroxyurea	HYDROXYUREA	CAPSULE	Y
hydroxyurea	HYDROXYUREA	CAPSULE	Y
glutamine	ENDARI	POWD PACK	N
hydroxyurea	DROXIA	CAPSULE	N
hydroxyurea	SIKLOS	TABLET	N
crizanlizumab-tmca	ADAKVEO	VIAL	N
voxelotor	OXBRYTA	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 64 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 December 23, 2021

Search Strategy:

#	Searches	Results
1	hydroxyurea.mp. or Hydroxyurea/	12708
2	glutamine.mp. or Glutamine/	46513
3	crizanlizumab.mp.	50
4	voxelotor.mp.	72
5	1 or 2 or 3 or 4	59243
6	limit 5 to (english language and humans and yr="2020 -Current")	1745
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	64

Appendix 4: Key Inclusion Criteria

Population	Patients with sickle cell disease
Intervention	Therapies for sickle cell
Comparator	Placebo or active treatment
Outcomes	Hemoglobin response, blood transfusions, stroke, vaso-occlusive crisis, hospitalizations, pain scores
Timing	Symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Sickle Cell Anemia Drugs

Goal(s):

- Approve the use of drugs for sickle cell disease for medically appropriate indications funded by the OHP.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs or non-preferred formulations (pharmacy administered claims)
- Crizanlizumab (pharmacy or provider administered claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a renewal request for voxelotor, crizanlizumab or l-glutamine (ENDARI)?	**Yes:** Go to renewal criteria below.	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products/formulations do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Has the patient failed a 3-month trial of hydroxyurea at stable doses,) or have contraindications to hydroxyurea?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; Recommend trial of hydroxyurea (stable dose for 3 months)
7. Is the request for voxelotor and the patient is 4 years or older?	**Yes:** Go to #8	**No:** Go to #9
8. Does the patient have a hemoglobin level of 10.5 g/dL or less AND have a history of at least 1 pain crisis in the last 12 months?	**Yes:** Approve for up to 6 months. Record baseline hemoglobin value.	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for crizanlizumab and the patient is 16 years or older?	**Yes:** Go to #10	**No:** Go to #11

Approval Criteria		
10. Has the patient had at least 2 pain crises in the last 12 months?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the request for L-glutamine (ENDARI) and the patient is 5 years or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient had at least 2 pain crises in the last 12 months?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for a first renewal of voxelotor?	**Yes**: Go to #2	**No:** Go to #4
2. Has the patient had an increase in hemoglobin from baseline hemoglobin level since starting voxelotor?	**Yes:** Approve for up to 12 months.	**No:** Go to #3
3. Is the request for subsequent renewals (renewals beyond the first year) of voxelotor and the patient has stable hemoglobin levels?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for a renewal of crizanlizumab?	**Yes**: Go to #5	**No:** Go to #6
5. Has the patient demonstrated improvements from baseline since starting crizanlizumab treatment?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a renewal of L-glutamine (ENDARI)?	**Yes:** Go to #7	**No:** See above for initial approval criteria.
7. Has the patient had a reduction in at least one annual pain crisis from baseline before L-glutamine treatment?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

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Drug Class Literature Scan: Fabry Disease

Date of Review: April 2022

Date of Last Review: September 2019
Literature Search: 01/01/2019 – 01/14/2022

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

Conclusions:
- No new high-quality systematic reviews or guidelines were published since the last Fabry Disease class update.
- Fabrazyme (agalsidase beta) received expanded FDA approval in March 2021 for use in patients aged 2 years and older with confirmed Fabry disease.[1] Prior to the expanded indication approval, the manufacturer's label stated the safety and effectiveness of agalsidase beta had not been established in pediatric patients less than 8 years of age.[2]

Recommendations:
- Revise prior authorization (PA) criteria to reflect expanded indication for agalsidase beta.

Summary of Prior Reviews and Current Policy
- Therapeutic agents to manage the lysosomal storage disorder Fabry disease were reviewed by the Pharmacy and Therapeutics (P & T) Committee in September 2019. Fabry disease is a funded condition on line 60 (metabolic disorders) of the Health Evidence Review Commission (HERC) prioritized list of health services.[3] After review, the committee designated agalsidase beta and migalastat as non-preferred agents on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP) and approved PA criteria for the Fabry disease treatments to ensure use according to FDA-approved indications (**Appendix 4**). At the time of 2019 review, there was insufficient evidence for the effectiveness of agalsidase in delaying the onset, or reducing the incidence and severity, of Fabry disease-related complications, and its impact on long-term survival remained unclear. Published data were not yet available on the effects of migalastat in patients with more advanced Fabry disease and with duration of therapy beyond 2 years.[4] There was insufficient data regarding the long term clinical outcomes of migalastat therapy or comparison with agalsidase beta.
- Since 2020, 60 patients under the Oregon Health Plan had claims associated with Fabry disease. Of these 60 patients, 3 were enrolled in Fee-For-Service (FFS), 53 were enrolled in a Coordinated Care Organization (CCO), and 4 patients were no longer eligible. There have been no pharmacy claims for migalastat in the past 12 months in FFS or CCO populations. In 2021, there were 13 patients in the CCO population with physician administered claims for agalsidase beta.

Author: Deanna Moretz, PharmD, BCPS

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 literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:
After review, 1 systematic reviews was 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).[5]

New Guidelines:
High Quality Guidelines: No new guidelines have been published or updated since the last Fabry Disease class update in 2019.

Additional Guidelines for Clinical Context:
In 2020, the National Society of Genetic Counselors (NGSC) published a focused revision for the 2013 Fabry Disease Practice Guidelines.[6] New information related to newborn screening, disease incidence, and treatment were provided to reflect current knowledge of Fabry Disease.[6] Guidance for free Fabry Disease diagnostic screening was added to the report. Migalastat indications, dosing and associated adverse effects were described. Finally, a summary of adverse outcomes associated with Fabry Disease and strong guidance to initiate enzyme replacement therapy in childhood to reduce disease impact were discussed.[6]

After review, 0 guidelines were excluded due to poor quality.

New Indications:
Fabrazyme (agalsidase beta) received expanded FDA approval March 2021 for use in patients aged 2 years and older with confirmed Fabry disease.[1] Prior to the expanded indication approval, the manufacturer's label stated the safety and effectiveness of agalsidase beta had not been established in pediatric patients less than 8 years of age.[2] The safety and effectiveness of Fabrazyme have been established in pediatric patients based on adequate and well-controlled studies in adults and a single-arm, open-label study in 16 pediatric patients (14 males, 2 females) with Fabry disease aged 8 to 16 years.[1] Additional data in 24 patients with Fabry disease aged (mean age 12 years) provided support for use in pediatric patients.[7]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Agalsidase beta	FABRAZYME	03/11/2021	Warnings and Precautions	In clinical trials and post marketing safety experience with FABRAZYME, approximately 1% of patients developed anaphylactic or severe hypersensitivity reactions during FABRAZYME infusion. Four serious infusion-associated reactions occurred in 3 patients during FABRAZYME infusions, including bronchospasm, urticaria, hypotension, and development of FABRAZYME-specific antibodies. Other infusion-associated reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus.[1] Higher incidences of hypersensitivity reactions were observed in adult patients with persistent anti-FABRAZYME antibodies and in adult patients with high antibody titer compared to that in antibody negative adult patients.[1] Physicians should consider testing for IgE antibodies in patients who experienced suspected hypersensitivity reactions and consider the risks and benefits of continued treatment in patients with anti-FABRAZYME IgE antibodies. There are no marketed tests for antibodies against FABRAZYME. If testing is warranted, contact Genzyme Corporation at 1-800-745-4447.[1] Patients who have had a positive skin test to FABRAZYME or who have tested positive for FABRAZYME-specific IgE antibody have been rechallenged with FABRAZYME using a rechallenge protocol. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.[1] Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion. The incidence of infusion- associated reactions was higher in patients who were positive for anti-FABRAZYME antibodies than in patients who were negative for anti-FABRAZYME antibodies.[1]
Migalastat	GALAFOLD	9/25/2020	Use in Specific Populations	<u>Pregnancy Exposure Study</u> There were 3 pregnant women with Fabry disease exposed to GALAFOLD in clinical trials. As such, the available data are not sufficient to assess drug associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed.[8]

				Lactation There is a study that collects data on effects of GALAFOLD on lactation for women with Fabry disease and their neonates and infants up to 1 year of age who are exposed through breast milk. Healthcare providers are encouraged to register patients or obtain additional information by contacting the Pregnancy Coordinating Center at 1-888-239-0758, email fabrypregnancy@ubc.com, or visit www.fabrypregnancyregistry.com.[8]

References:

1. FABRAZYME (agalsidase beta) for injection. Prescribing Information. Cambridge, MA; Genzyme Corporation. March 2021.
2. FABRAZYME (agalsidase beta) IV Injection Prescribing Information. Genzyme Corporation; Cambridge, MA. December 2018.
3. Oregon Health Authority, Oregon Health Evidence Review Commission. Prioritized List of Health Services. 1/1/2019. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx. Accessed August 5, 2019.
4. Center for Drug Evaluation and Research. Galafold Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208623Orig1s000MultidisciplineR.pdf Accessed July 24, 2019.
5. Sheng S, Wu L, Nalleballe K, et al. Fabry's disease and stroke: Effectiveness of enzyme replacement therapy (ERT) in stroke prevention, a review with meta-analysis. *Journal of Clinical Neuroscience.* 2019;65:83-86.
6. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. *J Genet Couns.* 2020;29(5):715-717.
7. Ries M, Clarke JT, Whybra C, et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics.* 2006;118(3):924-932.
8. GALAFOLD (migalastat) oral capsules. Prescribing Information. Cranbury, NJ; Amicus Therapeutics, Inc. 12/21.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
agalsidase beta	FABRAZYME	VIAL	N
migalastat	GALAFOLD	CAPSULE	N

Appendix 2: New Comparative Clinical Trials

A total of 16 citations were manually reviewed from the initial literature search. After further review, 16 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 1 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 14, 2022

1. Fabry Disease/ 3037
2. alpha-Galactosidase/ 2297
3. Migalastat.mp. 138
4. 2 or 3 2355
5. 1 and 4 1494
6. limit 5 to (english language and humans) 1301
7. limit 6 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review") 16

Fabry Disease

Goal(s):
- Ensure medically appropriate use of drugs for Fabry Disease

Length of Authorization:
- Up to 12 months

Requires PA:
Agalsidase beta (pharmacy and physician administered claims) and migalastat

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the provider a specialist in managing Fabry disease?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for migalastat?	**Yes:** Go to # 7	**No:** Go to # 10
7. Does the patient have a mutation that is amenable to migalastat therapy as confirmed by a genetic specialist?	**Yes**: Got to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently receiving agalsidase beta?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 9
9. Is the patient 18 years of age or older?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. Migalastat is only FDA-approved for use in adults.
10. Is the patient a male at least 2 years of age with diagnosis of Fabry disease confirmed by genetic testing or deficiency in alpha-galactosidase A enzyme activity in plasma or leukocytes?	**Yes:** Go to # 11	**No:** Go to # 12
11. Does the patient have end stage renal disease requiring dialysis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
12. Is the patient a female at least 2 years of age and a documented Fabry disease carrier confirmed by genetic testing with significant clinical manifestations of Fabry disease such as: • Uncontrolled pain that interferes with quality of life • Gastrointestinal symptoms that are significantly reducing quality of life and not attributable to other pathology • Mild to moderate renal impairment (GFR > 30 mL/min) • Cardiac disease (left ventricular hypertrophy, conduction abnormalities, ejection fraction< 50%, arrhythmias) • Previous stroke or TIA with retained neurologic function	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement in one of the following: • Renal function • Pain Scores • Quality of Life measurement • Cardiac function • Neurologic status • Growth and development in children	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/22 (DM); 9/19 (DM)
Implementation: 11/1/19

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

New Drug Evaluation: vosoritide injection, for subcutaneous use

Date of Review: April 2022
Generic Name: vosoritide

End Date of Literature Search: 1/31/2022
Brand Name (Manufacturer): VOXZOGO™ (Biomarin Pharmaceutical Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy and effectiveness of vosoritide in reducing symptoms, avoiding complications, or improving functional outcomes in patients with achondroplasia?
2. What are the harms of vosoritide in the treatment of patients with achondroplasia?
3. Are there subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from vosoritide therapy?

Conclusions:

- There was low quality evidence from one published study that reported treatment with vosoritide was associated with a statistically significant least-squares (LS) mean change in annualized growth velocity (AGV) compared with placebo (LS mean treatment difference 1.57 cm/year [95% CI, 1.22 to 1.93; p<0.0001]) at 52 weeks.[1,2] It is unclear if a change of 1.57 cm in AGV is clinically significant and whether treatment with vosoritide for achondroplasia leads to sustained AGV improvements throughout a child's natural growth period. The effects of vosoritide on final height, proportional growth, or other areas of clinical significance such as reduced symptoms, avoidance of medical complications, or improvements in functionality of achondroplasia patients are unknown.
- There is low quality evidence of no significant difference in discontinuations due to adverse events between vosoritide versus placebo, but a higher rate of injection site reactions (70% vs 43%, respectively). The most common adverse events in vosoritide treatment compared to placebo, respectively, were vomiting (27% vs. 20%), urticaria (25% vs. 10%), arthralgia (15% vs. 7%), hypotension (13% vs. 5%), gastroenteritis (13% vs. 8%), diarrhea (10% vs. 3%), dizziness (10% vs. 3%), ear pain (10% vs. 5%), and influenza (10% vs. 5%).[3] The long-term safety of vosoritide unknown as the required follow-up open-label study to evaluate the effects of vosoritide on final adult height, disproportionality, bone age, and safety endpoints in children with achondroplasia has yet to be completed.
- Outcome conclusions specific to race and ethnicity are insufficient due to variations of results, lack of statistical significance with many comparisons, and small subgroup sizes. The results are most applicable to white patients with achondroplasia ages 5 to 15 years which may not adequately represent diversity within the Oregon Medicaid population. There is insufficient evidence to evaluate the use of vosoritide in the treatment of other subpopulations with regard to gender, comorbidities, disease duration or severity.

Recommendations:

- Create prior authorization criteria for vosoritide to ensure appropriate use.

Author: David Engen, PharmD

Background:
Achondroplasia is an inherited, autosomal dominant skeletal dysplasia characterized by disproportionate growth and severe short stature. [4] The disorder is caused by a gain of function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene region located on chromosome 4.[4] In most cases, the mutation is spontaneous and increases in frequency when the father is 35 years of age or older.[5,6] In addition to small stature, achondroplasia often leads to other serious neurological, musculoskeletal, cardiopulmonary, and metabolic complications such as subdural hematomas, cervicomedullary compression, restrictive pulmonary disease, spinal stenosis, obesity, sleep apnea, and other impairments of body structure and function.[7-11] Achondroplasia affects approximately 1 in 25,000 births or roughly 250,000 individuals worldwide.[12]

Bone formation and long bone elongation is a complex process that begins in embryonic development and involves numerous regulatory pathways.[13] In a process known as endochondral ossification, mesenchymal cells differentiate into the chondrocytes of cartilage which are used as a blueprint for future bone formation.[13] Regulation of endochondral bone growth involves the multifaceted interaction of many signaling molecules and receptors such as fibroblast growth factors (FGFs) and fibroblast growth factor receptor (FGFR) kinases.[14] FGFs and FGFRs also help regulate many cellular functions such as proliferation, differentiation, angiogenesis, and tissue repair.[14] FGFR3 has been shown to be a negative regulator of endochondral bone development by shortening the cell proliferation stage and accelerating terminal differentiation of chondrocytes.[14] In patients with achondroplasia, mutations on FGFR3 gene result in over-activation of FGFR3 which disrupts normal regulation of chondrocyte cell signaling and leads to impaired bone growth. [15,16]

Although diagnosis of achondroplasia typically takes place in early infancy, the availability of prenatal ultrasound has made a clinical diagnosis possible as early as the third trimester of pregnancy.[17,18] Patients with achondroplasia generally present with macrocephaly and an upper to lower body segment ratio higher than in children without achondroplasia.[19] Patients also show signs of disproportionately short extremities along with a nearly normal trunk, short fingers, hypermobile hips and knees, hypotonia, and the later development of lumbar lordosis and bow legs.[7,13] There are usually no significant effects on intramembranous ossification in areas such as the skull, face, clavicles, and other flat bones.[18] In the neonatal stage, patients with achondroplasia display an abnormally small pelvis, shortened long bones, and a relatively large and prominent cranium[18] Confirmation of an achondroplasia diagnosis requires radiographic assessment.[18] Genetic testing is not typically necessary for diagnosis but can be obtained to confirm a prenatal diagnosis.[17] Almost all patients with achondroplasia will have a c.1138G>A gene mutation.[4]

Patients with achondroplasia are of normal intelligence and usually able to live independent, productive lives.[20] However, developmental milestones can be delayed, and some studies suggest that there may be a 10-year reduction in overall life-expectancy.[21] Therefore, early care management of patients with achondroplasia is often overseen by a pediatric neurologist or endocrinologist.[7] Prompt recognition of achondroplasia is important for effective management as early intervention strategies may minimize or even prevent serious health complications.[22] For example, acute brainstem compression may occur in infants with achondroplasia which puts them at increased risk of sudden death.[23] In these cases, it is recommended that a rapid neurologic history and neurologic examination is performed followed by imaging, polysomnography, and possible suboccipital decompression surgery.[24] Various growth curves specific to achondroplasia have been published which not only assist clinicians in tracking height and weight, but also help them anticipate and test for known complications at key stages in the disease.[13,25] Body mass is routinely monitored due to the potential for exacerbation of obstructive sleep apnea and spinal stenosis.[22] Other problems such as a rapidly enlarged head size or head size above the 95th percentile along with symptoms of increased pressure may indicate communicating hydrocephalus and warrant surgical shunting.[26] Surgical techniques to lengthen limbs have been employed, they are costly, not without risk, and often have significant social ramifications.[27] Newer techniques such as magnetic rodding technologies have been successful at reducing the risk of infection and scarring.[28] Therapy focused on improvements in linear height through surgical intervention or other means are still controversial as many individuals with

achondroplasia are taught to embrace and celebrate their uniqueness rather than looking at the condition as a disability.[28] Nonetheless, some patients with achondroplasia continue to suffer with depression, anxiety, and low self-image due to their condition. [15,29] The 36-item Short-Form Health Survey (SF-36) is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[30] The complete SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section and range from 0-100 where lower scores indicate more disability.[31] Some achondroplasia intervention studies have suggested SF-36 Physical Functioning domain scores improve with greater height, but the SF-36 has not been validated for use in patients with achondroplasia.[32,33] Cervical cord compression, cardiorespiratory function, metabolic monitoring, and neurocognitive development must all be closely monitored to prevent serious long-term complications in the patient with achondroplasia.[7]

There is currently no standard of care for the management of patients with achondroplasia, and there is limited evidence-based literature published to assist clinicians and caregivers. There is no known cure for achondroplasia, and 2020 practice guidelines from the American Academy of Pediatrics focus on identification of patients at high risk of developing complications.[34] Monitoring recommendations are stratified by age and include recommendations for diagnostic procedures, genetic counseling, and type of medical evaluation.[34] Most guideline recommendations were based on expert opinion. Other guideline limitations included lack of reporting for stakeholder involvement, method of consensus, search terms, detailed search strategy and inclusion/exclusion criteria. There was insufficient comparative evidence to guide recommendations on first-line medical therapy. The American Academy of Pediatrics noted that treatment guidance in the report does not indicate an exclusive course of treatment or serve as a standard of medical care so accounting for variations and individual circumstances may be appropriate.[34]

Clinical trials in patients with achondroplasia often evaluate outcomes such as improvements in final height, weight, and proportionality.[2] Disproportionality due to the extreme shortness of extremities compared to the trunk may be assessed using measurements of upper to lower body segment ratios.[1,19,25] For example, a larger ratio between sitting height and leg length may be associated with decreased mobility.[19] To monitor growth, specialized charts have been created for children with achondroplasia since their height advances considerably below normal curve area.[19] Deficits in growth in terms of annualized growth velocity (AGV) from infancy to adolescence are often tracked and compared to population norms.[19] Some studies have used these values and converted measurements to an age- and sex-appropriate score known as a height z-score which allows a comparison with normal references.[2,19] A negative z-score value such as -2 would be interpreted as a raw score 2 standard deviation lower than the mean average for a particular age and sex.[19] Clinically relevant outcomes in patients with achondroplasia include final height, functional improvement, and avoidance of long-term disease complications but no minimal clinically important difference has been established in these areas for this population. Research investigating whether there may be a correlation between height z-score and negative outcomes such as spinal cord compression or stenosis in patients with achondroplasia is ongoing.[35]

In 2022, vosoritide was FDA approved for achondroplasia based on the intermediate clinical endpoint of annualized growth velocity (AGV) and changes in height Z-scores. Vosoritide is a recombinant human C-type natriuretic peptide (CNP) that, when bound to NPR-B, helps regulate the overactive FGFR3 pathway which may stimulate chondrocyte proliferation and increase bone growth.[36-38] The effect of vosoritide on other clinically important endpoints related to abnormal bone growth have not been evaluated.[1]

In the Oregon Medicaid population between 1/1/2021 and 12/31/2021, there were fewer than 55 individuals with the diagnosis of achondroplasia (Q77.4), and approximately 15% of whom were part of the Fee-for-service (FFS) population.

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:

Vosoritide 15 mcg/kg subcutaneous injection daily is indicated for the treatment of achondroplasia in pediatric patients who are 5 years of age or older with open epiphyses.[1] Vosoritide was studied in one 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial (study 111-301) to determine efficacy and safety in the treatment of achondroplasia in 121 pediatric patients ages 5 to 17 years old.[1,2] Enrolled patients had completed a minimum 6-month lead-in observational growth study, were ambulatory, and had a diagnosis of ACH verified by genetic testing.[1,2] Patients were excluded if they had radiographic evidence of closed epiphyseal plates or growth velocity <1.5 cm/year, planned bone surgery, previous fracture of long bones or spine in prior 6 months, treatment with growth stimulant drugs in prior 6 months or oral corticosteroids in prior 12 months, symptomatic hypotension, chronic therapy with antihypertensive medications, diagnosed with cardiovascular disease, untreated sleep apnea, or any medical conditions known to affect growth.[1,2] The primary endpoint was the change from baseline in annualized growth velocity (AGV) at week 52.[1,2] Key secondary endpoints were change from baseline in height Z-score and upper to lower body segment ratio at week 52.[1,2] The upper to lower body segment ratio was calculated by the following: sitting height (cm)/[standing height (cm) – sitting height (cm)].[1] The mean age of enrolled patients was 8.7 years, and some differences were noted between groups for age ranges of 5 to 8-years (51% vosoritide vs. 39% placebo) as well as 8 to 11-years (28% vosoritide vs. 39% placebo).[1,2] Overall, characteristics were generally balanced between groups, and most subjects were prepubertal with Tanner Stage of 1 (79%), had a mean AGV of 4.16 cm/year, and had a standard deviation score (SDS)/height z-score of -5.13 at baseline.[1,2] Seventy-one percent of patients were white, almost 20% were Asian, and about 3-5% Black or African American.[1,2]

Vosoritide-treated patients demonstrated a statistically significant least-squares mean change in AGV of 1.4 cm/year compared to -0.17 cm/year in the placebo group (LS mean treatment difference 1.57 cm/year [95% CI, 1.22 to 1.93; p<0.0001]).[1,2] There was also a LS mean difference in SDS/height Z-score which favored vosoritide over placebo (0.28 [95% CI, 0.17 to 0.39; p<0.001]).[1,2] There was no statistically significant LS mean change in upper to lower body segment ratio compared to baseline.[1,2] The clinical significance of these relatively modest differences in height-related outcomes is unclear.

An ongoing, phase 3, open-label extension trial (study 111-302) was initiated for completers of study 111-301.[1,39] All participants received vosoritide at a dose of 15.0 µg/kg/day and were to be followed for either 5 years or until their near final adult height was reached. No prespecified statistical inference was performed, but trends in average AGV, height Z-score, and upper-to-lower body segment ratio were observed.[1,39] Fifty-six patients in the original vosoritide group continued vosoritide (vos/vos) treatment, while 61 subjects in the original placebo group were switched to vosoritide (pbo/vos).[1,39] Based on the FDA full analysis set, annualized growth velocity in the vos/vos arm was reported to increase from a baseline of 4.26 cm/year to 5.67 cm/year at week 52, followed by 5.57 cm/year at week 104.[1] For patients in the pbo/vos arm, baseline AGV was reported to decline from 4.06 cm/year to 3.94 cm/year at 52 weeks but after the switch to vosoritide the AGV increased to 5.43 cm/year at week 104.[1] Mean SDS/height z-scores for standing height was converted to an age- and sex-appropriate Z-score for comparison.[1,39] These results are summarized in **Table 1.**

Table 1. 12-month Interval AGV (cm/year) Over Time – Full Analysis Set[1]

	Week 0 (baseline)		Week 52		Week 104		Change from Baseline to 1 year		Change from 1 year to 2 years	
	Vosoritide (N=60)	Placebo (N=61)	Vosoritide (N=58)	Placebo (N=61)	Vos/Vos (N=52)	PBO/Vos (N=54)	Vosoritide	Placebo	Vos/Vos	PBO/Vos
Mean AGV (cm/year)	4.26	4.06	5.67	3.94	5.52	5.43	1.41 (0.96 to 1.86)*	-0.12 (-0.56 to 0.33)*	- 0.14 (-0.50 to 0.22)*	1.66 (1.22 to 2.10)*
Mean SDS/height Z-score	-5.13	-5.14	-4.85	-5.14	-4.54	-4.89	0.24 (0.15 to 0.32)*	-0.005 (-0.077 to 0.067)*	0.21 (0.11 to 0.30)*	0.23 (0.14 to 0.32)*

**=95% CI for mean change from baseline is from paired t-test between visits.*

Trial Limitations

The trial included the use of AGV and changes in height Z-scores which are intermediate clinical endpoints. It is unclear if a change of 1.57 cm in AGV is clinically significant and whether treatment with vosoritide for achondroplasia leads to sustained AGV improvements throughout a child's natural growth period. It is unknown to what extent age influenced clinical response rate as patients in the vosoritide group appeared to be slightly younger than those in the placebo group. The long-term effects of vosoritide on final height, proportional growth, or other areas of clinical significance such as reduced medical complications associated with achondroplasia, functionality, or activities of daily living are unknown. The results of the study are most applicable to patients with open epiphyses who are still growing as patients with AGV of <1.5cm/year were excluded. Also, it is unknown if the vosoritide study results would apply to those with more severe disease as patients were required to be ambulatory and not have a prior fracture. In addition, patients are typically diagnosed at birth (or prior) but vosoritide was not studied in those <5 years of age. There may be unknown mental health consequences of focused efforts to solely improve linear growth since children with achondroplasia are often able to live healthy and productive lives regardless of physical height and are frequently taught to think of their condition as a difference to be celebrated and not as a person with a disability or disease. Outcomes with a linear growth focus may need to be united with validated scales that assess health-related quality of life improvements to help determine the impact on mental health. Larger and longer trials are required before the long-term effects and potential risks of vosoritide therapy are known.

Clinical Safety:

Trial attrition was low overall with 2 discontinuations due to anxiety and pain in the vosoritide group (1.7%) and none in the placebo group.[1,2] Although there were no significant differences in discontinuations due to adverse events between groups, a higher rate of injection site reactions was observed in the vosoritide group compared to placebo (70% vs 43%, respectively).[1] Besides injection site reactions (erythema, swelling, and urticaria), the most common adverse events in vosoritide treatment compared to placebo were gastrointestinal events (vomiting, gastroenteritis, and diarrhea) arthralgia, hypotension, dizziness, ear pain, and influenza.[1-3] The incidence of serious adverse events were few and occurred at similar rates in vosoritide and placebo groups.[1-3] **Table 2** presents the frequency of common adverse reactions.[1,3]

Table 2. Adverse Reactions Occurring in ≥10% Vosoritide-Treated Patients and >5% More Frequently than in Placebo-Treated Patients[1,3]

	Vosoritide (N=60) n (%)	Placebo (N=61) n (%)
Injection site erythema	45 (75)	42 (69)
Injection site swelling	37 (62)	22 (36)
Vomiting	16 (27)	12 (20)
Injection site urticaria	15 (25)	6 (10)
Arthralgia	9 (15)	4 (7)
Hypotension	8 (13)	3 (5)
Gastroenteritis	8 (13)	5 (8)
Diarrhea	6 (10)	2 (3)
Dizziness	6 (10)	2 (3)
Ear Pain	6 (10)	3 (5)
Influenza	6 (10)	3 (5)

There were no deaths in either the vosoritide or placebo study groups.[1,3] The FDA labeling did not identify any contraindications to vosoritide therapy, however, there were many trial exclusions for patients with various cardiovascular risks, those on chronic therapy with antihypertensive medications, and patients with symptomatic hypotension.[3] Use of vosoritide in patients with eGFR less than 60 ml/min/1.73 m^2 is not recommended.[1,3] As a post-marketing condition of approval, the FDA has required that the manufacturer continue the long-term, open-label study to evaluate the effects of vosoritide on final adult height, disproportionality, bone age, and safety endpoints related to the drug (e.g. blood pressure effects) or to the disease that may improve or worsen with long-term treatment (e.g. bone deformities, neurological complications, sleep apnea, etc.).[1]

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Final Height
2) Disease progression and complications (e.g., cervicomedullary compression, spinal stenosis, etc)
3) Health-related quality of life and function
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annualized growth velocity (AGV; cm/year) at Week 52

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) that inhibits the FGFR3 signaling pathway and consequently, stimulates chondrocyte proliferation and differentiation which promotes linear growth.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd: 2880 mL/kg to 3020 mL/kg; increases with increasing body weight; Protein Binding: Not available
Elimination	Not available
Half-Life	SubQ, multiple-dose, 15 mcg/kg: 21 minutes to 27.9 minutes
Metabolism	Catabolic pathways with degradation into small peptide fragments and amino acids

Abbreviations: FGFR3=fibroblast growth factor receptor 3; SubQ=subcutaneous; Vd=volume of distribution

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Savarirayan et al.[1, 2]	1. vosoritide 15 mcg/kg SC daily 2. placebo 52 weeks	Demographics: 1. Mean age: 8.7 years (range 5.1 to 14.9 years) 2. Ethnic group: -White/Caucasian 71% -Asian 19% -Black/African American 5% 3. Mean baseline AGV (cm/year): -Vosoritide: 4.26 -Placebo: 4.06 4. Mean baseline height SDS/Z-score: -Vosoritide: -5.13 -Placebo: -5.14 5. Mean Upper to lower body segment ratio: -Vosoritide: 1.98 -Placebo: 2.01 6. Sleep apnea -Vosoritide 45% -Placebo 51% 6.Cervical spinal stenosis -Vosoritide 12% -Placebo 3%	ITT: 1. 60 2. 61 Attrition: 1. 2 (2%) 2. 0 (0%)	Primary Endpoint: LS mean change from baseline in AGV (cm/year) 1. 1.4 2.- 0.17 LSMD 1.57 (95% CI, 1.22 to 1.93); p<0.0001 Secondary Endpoints: Change from baseline in height Z-score 1. 0.27 2. -0.01 LSMD 0.28 (95% CI 0.17 to 0.39); p <0.0001 LS mean change in upper to lower body segment ratio compared to baseline -No statistically significant difference between groups	N/A	Serious Adverse Events 1. 3 (5%) 2. 4 (7%) ARD -1.6 (95%CI, -9.9 to 6.7) Any Adverse Event 1. 59 (98%) 2. 60 (98%) ARD -0.1 (95% CI, -4.6 to 4.4) Injection site reaction 1. 42 (70%) 2. 26 (43%) ARD 27.4 (95% CI, 10.4 to 44.4)	NS NS NNH 4	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomly assigned 1:1 to receive either vosoritide or matched, identical placebo. Randomization was done with the use of an interactive, automated voice-response or web response System. Baseline characteristics were similar between groups except higher percentage white and non-Hispanic/Latino patients in vosoritide group, and overall younger patients in vosoritide group. Performance Bias: Low. Participants, investigators, caregivers administering injections were all masked to group assignment. Electronic data capture system was used to collect study data at each site. Detection Bias: Low. Assessors analyzing outcome data were all masked to group assignment. Attrition Bias: Low. <5% attrition overall and in either group. All randomized and consented patients were included, and ITT analysis performed for both groups. Reporting Bias: Low. Trial protocol was followed. Other Bias: Unclear. Study was funded by manufacturer. Many major authors served as consultants for or received research funding from manufacturer.

		Key Inclusion Criteria: -completed 6-month growth study -ambulatory -genetically verified ACH diagnosis Key Exclusion Criteria: -evidence of closed growth plates or growth velocity <1.5 cm/year -planned bone surgery -severe untreated sleep apnea -medical conditions or treatments known to affect growth -previous fracture of long bones or spine in prior 6 months -treatment with growth stimulant drugs in prior 6 months or oral corticosteroids in prior 12 months -symptomatic hypotension -chronic therapy with antihypertensive medications -diagnosed with cardiovascular disease						**Applicability**: Patient: Results most applicable to white patients with achondroplasia ages 5 to 15 years. Extensive exclusion criteria. Unknown effects on patients with cardiovascular risks, on chronic therapy with antihypertensive medications, or patients with symptomatic hypotension, etc. Intervention: Vosoritide dose appropriately determined from a phase 2 study. Comparator: Placebo is appropriate comparator to determine efficacy. Outcomes: AGV surrogate marker to demonstrate drug efficacy in treatment of disproportional short stature at 52 weeks. The impact on long-term growth velocity, final height upon closed epiphyses, physical symptom or daily functioning improvement is unknown. Setting: 7 countries, 24 sites in 7 countries (Australia, Germany, Japan, Spain, Turkey, USA, and UK)
Abbreviations: ARD = absolute risk difference; ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; LS = least squares; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SC = subcutaneous; SDS = standard deviation score								

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Appendix 1: Prescribing Information Highlights

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

VOXZOGO (vosoritide) for injection, for subcutaneous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
VOXZOGO is a C type natriuretic peptide (CNP) analog indicated to increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------
- Ensure adequate food and fluid intake prior to administration. (2.1)
- Recommended dosage is based on patient's weight. Administer subcutaneously once daily. (2.2)
- Reconstitute prior to use. The injection volume is based on both patient's weight and concentration of reconstituted VOXZOGO. (2.2)
- Monitor growth and adjust dosage according to body weight. Permanently discontinue upon closure of epiphyses. (2.3)
- See full prescribing information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 0.4 mg, 0.56 mg, or 1.2 mg lyophilized powder in a single-dose vial for reconstitution. (3)

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

----------WARNINGS AND PRECAUTIONS----------
Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported. (5 1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>10%) are injection site erythema, injection site swelling, vomiting, injection site urticaria, arthralgia, decreased blood pressure, and gastroenteritis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment Not recommended in patients with eGFR < 60 mL/min/1.73 m^2. (8.6)

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

Revised: 11/2021

Vosoritide

Goal(s):

- Ensure medically appropriate use of approved agents for the treatment of achondroplasia in pediatric patients

Length of Authorization:

- Up to 12 months

Requires PA:

- Vosoritide

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:

Actual Body Weight	Vial Strength for Reconstitution*	Dose	Injection Volume
10-11 kg	0.4 mg	0.24 mg	0.3 mL
12-16 kg	0.56 mg	0.28 mg	0.35 mL
17-21 kg	0.56 mg	0.32 mg	0.4 mL
22-32 kg	0.56 mg	0.4 mg	0.5 mL
33-43 kg	1.2 mg	0.5 mg	0.25 mL
44-59 kg	1.2 mg	0.6 mg	0.3 mL
60-89 kg	1.2 mg	0.7 mg	0.35 mL
≥90 kg	1.2 mg	0.8 mg	0.4 mL

*=The concentration of vosoritide in reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL.
The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication based on diagnosis and current age restrictions?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
4. Is the prescribed agent being dosed according to actual body weight (ABW) as outlined in Table 1?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to Renewal Criteria	**No:** Go to #6
6. Is the agent prescribed by, or in consultation with, a pediatric endocrinologist, neurologist, or other prescriber specialized in the care of patients with achondroplasia or skeletal dysplasia?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documented evidence of a baseline measurement of annualized growth velocity (AGV) within the last 90 days AND, if male ≥15 years or female ≥13 years old, evidence of non-closure of epiphyseal plates?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a history of bone-related surgery or fracture of long bone or spine within the previous 6 months or planned bone surgery?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have a diagnosis of recurrent symptomatic hypotension with or without orthostasis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months

Renewal Criteria		
1. Is this an FDA approved indication based on diagnosis and current age restrictions?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is there documented evidence that the regimen is well tolerated with no adverse effects or drug toxicity?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documented evidence of adherence of at least 85% to the approved therapy regimen verified through claims history and/or provider assessment OR If adherence less than 85% of the time, there is documentation that the discontinuation was temporary due to the need for surgery or treatment of an infection?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is this the first renewal request?	**Yes:** Approve for 6 months	**No:** Go to #5
5. Is there documented evidence of an improvement in annualized growth velocity (AGV) ≥ 1.0 cm/year from baseline AND, if male ≥15 years or female ≥13 years old, evidence of non-closure of epiphyseal plates?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/22 (DE)
Implementation: TBD

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

New Drug Evaluation: efgartigimod alfa-fcab injection, for intravenous use

Date of Review: April 2022
Generic Name: efgartigimod alfa-fcab

End Date of Literature Search: 02/01/2022
Brand Name (Manufacturer): Vyvgart™ (Argenx)
Dossier Received: yes

Research Questions:

1. What is the evidence for efficacy and harms for efgartigimod when used as a treatment for generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive?
2. Are there specific subpopulations that would benefit or be at increased risk of harms with the use of efgartigimod?

Conclusions:

- Efgartigimod approval was based on one placebo-controlled, phase 3, manufacturer funded, 26-week, randomized controlled trial (RCT) in 167 adult patients with generalized MG. The primary outcome was conducted in patients who were seropositive for the AChR antibody (77% of enrolled patients).[1]
- There was low quality evidence that efgartigimod infusion was found to be more effective than placebo for the primary outcome of percentage of Myasthenia Gravis-Activities of Daily Living (MG-ADL) responders at week 8 (odds ratio [OR] 4.95; 95% confidence interval [CI], 2.21 to 11.53; P<0.001; absolute risk reduction [ARR] 38% / number needed to treat [NNT] 3).[1] Responders were defined as patients with a two or more point reduction in the MG-ADL total score compared to baseline that was maintained for four consecutive weeks, with the first reduction occurring no later than one week after the last infusion of the product after 4 weeks of initial treatment. Approximately, 70% of patients experienced the minimum point reduction in the MG-ADL to be classified as a responder with a clinically significant change.
- Adverse reactions occurring in 10% or more of patients treated with efgartigimod, and more frequently than placebo, are respiratory tract infections, headache and urinary tract infections. Serious adverse reactions occurred in 5% of efgartigimod patients versus 8% in the placebo group.[1] Efgartigimod transiently reduces IgG levels and should not be given if the patient has an active infection and immunization with live-attenuated or live vaccines is not recommended during treatment.[2]
- Exploratory analysis of subgroup populations (e.g., gender, age and MG-ADL score) demonstrated no differences in results compared to general findings.
- There is insufficient evidence for the use of efgartigimod in black women, in which there is a higher prevalence of MG compared to white women.

Recommendations:

- Designate efgartigimod as non-preferred on the preferred drug list (PDL) and subject to prior authorization (PA) criteria.

Author: Kathy Sentena, PharmD

Background:
Myasthenia gravis (MG) is an autoimmune disease that is rare with an incidence of 150 to 250 per million people. Females, 40 years and younger, are more commonly affected by MG than males and males 50 years and older have a higher incidence than females.[3] The pathophysiology of MG often involves autoantibodies against skeletal muscle nicotinic acetylcholine receptors.[4] Approximately 85% of patients with MG are AChR antibody positive.[5] To a lesser extent, muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related protein-4 (LRP4) are also involved. Myasthenia gravis affects antibody formation at the postsynaptic receptors at the neuromuscular junction causing weakness and disability involving ocular, bulbar, limb and respiratory muscles. Common symptoms may include ptosis, diplopia, facial weakness, dyspnea, dysphagia, dysarthria and weakness in the extremities and neck. Symptoms of MG can worsen after activity and improve upon rest.[6] In rare cases life-threatening respiratory failure, defined as a myasthenia crisis, can occur. The diagnosis of MG and the extent of disability is classified by the Myasthenia Gravis Foundation of America (MGFA) Classification Scale. The scale classifies patients according to class ranging from Class I (stable remission) to Class V (requiring intubation). It is not uncommon for patients with MG to also have associated comorbidities such as other autoimmune disorders, thymoma or myocarditis.[6]

Treatment determinants of MG involve the age of patient, respiratory or bulbar involvement, disease severity and progression. Current treatments target the amount of acetylcholine at the neuromuscular junction or to suppress the immune system to limit the production of autoantibodies.[3] Standard of care includes symptom management (e.g., acetylcholinesterase inhibition), chronic immunosuppressive therapy (e.g., glucocorticoids and nonsteroidal immunosuppressive drugs), and short-acting immunomodulating treatments (e.g., therapeutic plasma exchange and intravenous immune globulin [IVIG]) (**Table 1**).[4] Guidelines recommend treatment with pyridostigmine first-line for most patients with MG.[7] Corticosteroids or immunosuppressant therapy should be offered to patients who continue to have symptoms while taking pyridostigmine. There is a paucity of high quality evidence to guide immunosuppressant therapy in MG; however, azathioprine is recommended as the first-line immunosuppressant treatment based on moderate evidence.[7] Other immunosuppressants that are used for MG are: cyclosporine, mycophenolate mofetil, methotrexate and tacrolimus. If conventional therapies fail to control symptoms of MG, immunomodulatory therapies such as eculizumab or rituximab may be considered.[3] Eculizumab is Food and Drug Administration (FDA) approved for the treatment of MG and is recommended for severe, refractory, AChR antibody positive patients. Rituximab is recommended off-label with low-quality evidence of efficacy in patients who are MuSK antibody positive.[3,8] Oral methotrexate also has a role in treating MG as a steroid-sparing therapy in patients that have not responded to other steroid-sparing therapies.[8] Patients that present with severe disease or disease that is progressing rapidly should be treated as if in a myasthenic crisis using rapid therapies (e.g., therapeutic plasma exchange and IVIG). Thymectomy may be considered in some cases as a surgical option for patients with thymoma and lack of symptom control with anticholinesterase inhibitors with or without immunotherapies. There is large variability in the onset and time to maximal effect of treatments. Many medications, specifically those that effect neuromuscular transmission, can exacerbate MG and symptoms should be monitored for changes any time a new drug is initiated. Patients who test positive for MuSK have more success with glucocorticoids and respond less well to anticholinesterase therapies.[4]

Table 1. Medications to Treat Myasthenia Gravis[4]

Medication	Dose	Time of effect	Notes
Initial Therapy			
Pyridostigmine†	Adults: 30 mg 3 times daily orally Max dose is 120 mg every 4 hours while awake Children and adolescents: 0.5 to 1 mg/kg every 4-6 hours with meals Max dose is 7 mg/kg per 24 hours divided in 5 to 6 doses	Onset: 15 minutes Maximal effect: 2 hours	- Indicated for mild to moderate MG - Patient response is variable

Chronic Immunotherapies for patients requiring additional symptom management			
Prednisone	20 mg daily and increase by 5 mg every 3 to 5 days to a target dose of 60 mg per day orally Max dose of 80 mg per day	Onset: 2 to 3 weeks Maximal effect: 5 to 6 months	- Titrate dose over 4 to 8 weeks
Azathioprine*	50 mg daily for 2 to 4 weeks orally Titration of 50 mg every 2 to 4 weeks to maintenance dose of 2 to 3 mg/kg	Onset: 12 months Maximal effect: 1 to 2 years	- Considered first-line as a steroid sparing therapy
Mycophenolate mofetil*	2000 mg daily orally	Onset: 6 to 12 months Maximal effect: 1 to 2 years	- Often used first-line however evidence is less robust
Cyclosporine	5 mg/kg daily divided in 2 doses orally	Onset: 6 months Maximal effect: 12 months	- Effective in prednisone naïve and prednisone-dependent - Renal toxicity and drug interactions
Tacrolimus	3 to 8 mg per day orally	Onset: 6 months Maximal effect: 12 months	- Renal toxicity and drug interactions
Eculizumab†[7]	900 mg IV weekly for the first 4 weeks 1200 mg for the 5th dose 1 week later 1200 mg every 2 weeks thereafter	Onset: Less than 1 week Maximal effect: 3 weeks	- Boxed warning for life-threatening and fatal meningococcal infection - Only available through a Risk Evaluation and Mitigation Strategy (REMS) - Not indicated for MuSK antibody positive or LRP4 antibody positive patients.
Rapid Immunotherapies			
Plasmapheresis	Not applicable	Onset: 1 to 7 days Maximal effect: 1 to 3 weeks	- Reserved for seriously ill patients in the midst of myasthenic crisis
Intravenous immune globulin	2 g/kg IV given over 2 to 5 days	Onset: 1 to 2 weeks Maximal effect: 1 to 3 weeks	- Dose should be more spread over more days in individuals who have congestive heart failure or older adults
Key: * Glucocorticoid-sparing therapy; † FDA approved for treating myasthenia gravis Abbreviations: IV = intravenous; LRP4 = low-density lipoprotein receptor-related protein-4; MuSK = muscle-specific tyrosine kinase			

The goals of treatment for patients with MG are symptom management (neurological deficits), sustained remission and full functional capacity. One outcome commonly used in clinical trials to determine efficacy is the MG-ADL total score. The MG-ADL measures the impact of MG on daily function with scores ranging from 0 (normal function) to 3 (loss of ability to perform function). Total scores range from 0 to 24. The minimally clinically important difference (MCID) is 2 or more point increase in total MG-ADL score.[10] The Quantitative Myasthenia Gravis (QMG) assessment is also used to determine muscle weakness in patients who have MG, which is based on a 13-item, 4-point scale ranging from 0 to 39.[3] The MCID for the QMG is a 3 or more point reduction.[11]

There were 44 unique patients within fee-for-service (FFS) population with a diagnosis of MG within the last year. There is no PDL class for MG and 3 claims total for drugs FDA approved for MG (e.g., pyridostigmine, eculizumab and efgartigimod).

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:
Efgartigimod is a neonatal FC receptor blocker indicated for the treatment of gMG in adult patients who are anti-AChR antibody positive.[2] Efgartigimod reduces IgG subtypes without affecting the concentrations of other immunoglobulins or albumin.

Efgartigimod was studied in one, placebo-controlled, double-blind, phase 3 trial. One-hundred sixty seven patients who were classified as having MGFA class II to IV were randomized to efgartigimod 10 mg/kg or placebo infusion given as a 4-week treatment cycle of once weekly for 28 weeks (including a 2 week screening period). Additional cycles were administered according to clinical response which was determined when MG-ADL score was at least 5 (with >50% MG-ADL non-ocular related) and if the patient was an MG-ADL responder when they no longer had a clinically meaningful decrease compared to baseline (MG-ADL clinically meaningful improvement defined as having 2 point or greater improvement in total MG-ADL). Additional cycles were administered no sooner than 8 weeks from initiation of the previous cycle. A patient could receive a maximum of 3 cycles during the 26-week study. Patients enrolled in the study were predominately female (71%), white and MGFA Class III (suggesting moderate weakness). Fifty-seven percent of patients had undergone a thymectomy with differential rates in the efgartigimod group (70%) compared to placebo (43%). All patients were required to be on a stable dose of at least one treatment for gMG. At baseline 71% of percent of patients were on a steroid, 61% were on a non-steroidal immunosuppressant therapy and 51% were on both treatments.

The primary endpoint was the percentage of MG-ADL responders during cycle 1. Patients were considered MG-ADL responders if there was a 2 or more point reduction in the MG-ADL total score compared to baseline that was maintained for 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the product in cycle 1. The primary endpoint was assessed at 8 weeks and only included patients who were seropositive for the AChR antibody. The secondary endpoint was the percent of QMG responders during cycle 1 in the AChR antibody seropositive population. QMG responders were those who experienced a 3 or more point reduction in the total QMG score compared to baseline that was maintained for 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of efgartigimod in cycle 1.

A majority of patients (66%) received 2 cycles of efgartigimod. Fifty-six percent of patients completed just one cycle and 6% completed a third cycle (results not reported).[1] At 8 weeks, the number of MG-ADL responders was higher in the efgartigimod group (68% vs. 30%; ARR 38%/NNT 3). Patients that received a second cycle had similar results, with 71% of patient treated with MG-ADL responders in the efgartigimod group compared to 26% of patients treated with placebo. Findings for MG-ADL Responders in cycle 1 for all patients, regardless of AChR-Ab positivity, was higher in the efgartigimod group compared to placebo (ARR 38% / NNT 4). The majority of patients (77.8%) experienced a minimum improvement of 2 points in the MG-ADL score, indicating the minimum value to be considered clinically significant. Similar results were reported with the QMG score, with a minimum point change of 3 points occurring in 63% of patients treated with efgartigimod compared to 14% in the placebo group. For the secondary endpoint of percent of QMG responders in cycle 1, efgartigimod was more effective than placebo (OR 10.84; 95% CI, 4.18 to 31.20; $p<0.0001$; ARR 49%/NNT 2). Improvements were demonstrated from week 1 and maximum improvement for the primary endpoint and key secondary endpoints occurred at week 4. Exploratory subgroup analyses did not find any differences in results for gender, age or MG-ADL disability at baseline.

Limitations to the evidence include efficacy conclusions based on one, small study in adults with gMG. A higher incidence of thymectomy in the efgartigimod group may offer an advantage as patients that have undergone a thymectomy experience less muscle weakness and need for immunosuppressant drugs. Most

patients (86%) were on background immunosuppressant therapy (steroids and non-steroidal immunosuppressive therapies). There were more females enrolled in the study compared to males (75% vs. 25%); however, this is representative of the population diagnosed with gMG in this age group. Most patients experienced MG-ADL and QMG score changes that met the minimum point value to be considered clinically significant.

Clinical Safety:

Most common adverse reactions occurring in 5% or more of patients treated with efgartigimod are respiratory tract infections, headache, urinary tract infections, paresthesia and myalgia (**Table 2**). Serious adverse reactions occurred in 5% of efgartigimod patients (e.g., thrombocytosis, rectal adenocarcinoma, worsening MG, and depression) versus 8% in the placebo group (e.g., myocardial ischemia, atrial fibrillation and spinal ligament ossification). There were no deaths in either group. Treatment discontinuations due to adverse reactions were the same in efgartigimod and placebo treated patients (4% in each group). Efgartigimod infusion should be delayed if the patient has an active infection and patients should be monitored for infections while undergoing treatment.

Table 2. Adverse Reactions in Patients Treated with Efgartigimod compared to Placebo at an Incidence of 5% or more[2]

Adverse Reaction	Efgartigimod (N=84)	Placebo (N=83)
Respiratory tract infection	33%	29%
Headache (migraine and procedural)	32%	29%
Urinary tract infection	10%	5%
Paresthesia (oral hypoesthesia, hypoesthesia, and hyperesthesia)	7%	5%
Myalgia	6%	1%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of MG symptoms
2) Ability to perform activities of daily living
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Magnitude of change in MG-ADL

Table 3. Pharmacology and Pharmacokinetic Properties[2]

Parameter	
Mechanism of Action	Efgartigimod is a human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn), causing reductions of circulating IgG.
Oral Bioavailability	NA
Distribution and Protein Binding	Volume of distribution 15 to 20 L Protein binding not described
Elimination	Less than 0.1% recovered in the urine
Half-Life	80 to 120 hours
Metabolism	Degraded by proteolytic enzymes into small peptides and amino acids

Abbreviations: L – liter; NA – not applicable

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N∞	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Howard, et al[1] DB, PC, Phase 3, RCT	1. Efgartigimod 10 mg/kg (given as 4 infusions per cycle, 1 infusion per week)* 2. Placebo 26 week study	Demographics: Female: 71% Age: 47 years White: 85% Asian: 10% Time since MG diagnosis: 9 years MGFA class II: 39% MGFA class III: 58% MGFA class IV: 4% MG-ADL total mean score: 9.0 Previous thymectomy: 57% Acetylcholine receptor antibody-positive: 77% MG therapy at baseline - Steroid: 76% Any NSIST: 61% Steroid and NSIST: 52% Key Inclusion Criteria: - Ages 18 years and older with generalized MG - MG-ADL score of at least 5 (>50% non-ocular) - Stable dose of at least one treatment for MG Key Exclusion Criteria: - Rituximab or eculizumab in the previous 6 months before screening - Thymectomy in the previous 3 months - Intravenous immunoglobulin or plasma exchange within 1 month of screening - Active hepatitis B - Seropositive for hepatitis C - seropositive for HIV with low CD4 count - Serum IgG levels less than 6 g/L at screening - Pregnant	mITT: 1. 84 2. 83 PP: 1. 79 2. 73 Attrition: 1. 5 (6%) 2. 10 (12%)	Primary Endpoint: MG-ADL Responders in Cycle 1 for patients who are seropositive for the AChR antibody‡: 1. 44 (68%) 2. 19 (30%) OR 4.95 (95% CI, 2.21 to 11.53) P<0.001 Secondary Endpoint: Quantitative Myasthenia Gravis responders in cycle 1†: 1. 41 (63%) 2. 9 (14%) OR 10.84 (95% CI, 4.18 to 31.20) P<0.0001 MG-ADL Responders in Cycle 1 (all patients): 1. 57 (68%) 2. 31 (37%) OR 3.70 (95% CI, 1.85 to 7.58) P<0.0001	ARR 38%/ NNT 3 ARR 49% / NNT 2 ARR 31% / NNT 4	Serious Adverse Events: 1. 4 (5%) 2. 7 (8%) Discontinuations due to Adverse Events: 1. 3 (4%) 2. 3 (4%) Any Infection: 1. 39 (46%) 2. 31 (37%) Headache: 1. 24 (29%) 2. 23 (28%) Nasopharyngitis: 1. 10 (12%) 2. 15 (18%)	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via central interactive response technology via web and voice systems. Randomization stratified via acetylcholine receptor antibody, NSISTs and Japanese nationality. More patients in the efgartigimod had undergone thymectomy compared to placebo, 70% vs. 43%, respectively. Performance Bias: (Low) Matching placebo in identical containers. Participants, investigators and clinical staff blinded. Detection Bias: (Unclear) Outcome assessment not described. Attrition Bias: (Low) Attrition was low in both groups. Analysis was done on the mITT population. Handling of missing data was not described. Reporting Bias: (Low) Study followed original trial design. Other Bias: (High) Study was funded by the manufacture. Funding source had role in data collection, data interpretation and analysis. **Applicability**: Patient: The results of this trial are most applicable to patients taking immunosuppressive therapy, who were acetylcholine receptor antibody-positive and had moderate disease based on MG-ADL scores. Intervention: The dose of efgartigimod is appropriate based on phase 2 studies. Comparator: Active treatment comparison would be helpful to determine place in therapy. Outcomes: The primary outcome, although a subjective assessment of efficacy, has been used for other therapies seeking approval for use in gMG patients and is recommended by the FDA. Responders were defined based on minimum clinically important differences referenced in the literature. Setting: Fifty-six centers in 15 countries in North America, Japan and Europe.

Key: * All patients receive an initial cycle with subsequent cycles administered according to clinical response when MG-ADL score was at least 5 (with >50% MG-ADL non-ocular) and if the patient was an MG-ADL responder, no clinically meaningful decrease compared to baseline (MG-ADL clinically meaningful improvement defined as having 2 point or greater improvement in total MG-ADL); ‡‡ Patients were considered MG-ADL responders if there was a 2 or more point reduction in the MG-ADL total score compared to baseline that was maintained for 4 consecutive weeks, with the first reduction occurring no later than 1 week after the last infusion of the product in cycle 1† Quantitative Myasthenia Gravis (QMG) score is physician assessed with quantitative measures (clinically meaningful improvement defined as 3 or more point reduction); ∞ All patients, acetylcholine receptor antibody-positive and those were acetylcholine receptor antibody-negative.
Abbreviations: AchR = anti-acetylcholine receptor; ARR = absolute risk reduction; CI = confidence interval; ITT = intention to treat; MG = myasthenia gravis: MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NSIST = non-steroidal immunosuppressant therapy; NR = not reported; OR = odds ratio; PP = per protocol.

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Appendix 1: Prescribing Information Highlights

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

VYVGART ™ (efgartigimod alfa-fcab) injection, for intravenous use
Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------
VYVGART is a neonatal Fc receptor blocker indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. (1)

----------DOSAGE AND ADMINISTRATION----------
- Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle with VYVGART. (2.1)
- The recommended dosage is 10 mg/kg administered as an intravenous infusion over one hour once weekly for 4 weeks. In patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion. (2.2)
- Administer subsequent treatment cycles based on clinical evaluation; the safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established. (2.2)
- Must be diluted with 0.9% Sodium Chloride Injection, USP prior to administration. (2.3)
- Administer as an intravenous infusion over one hour via a 0.2 micron in-line filter. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 400 mg in 20 mL (20 mg/mL) single-dose vial. (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Infections: Delay administration of VYVGART to patients with an active infection. Monitor for signs and symptoms of infection in patients treated with VYVGART. If serious infection occurs, administer appropriate treatment and consider withholding VYVGART until the infection has resolved. (5.1)
- Hypersensitivity Reactions: Angioedema, dyspnea, and rash have occurred. If a hypersensitivity reaction occurs, discontinue the infusion and institute appropriate therapy. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 10%) in patients treated with gMG are respiratory tract infections, headache, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact argenx at 1-833-argx411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Closely monitor for reduced effectiveness of medications that bind to the human neonatal Fc receptor. When concomitant long-term use of such medications is essential for patient care, consider discontinuing VYVGART and using alternative therapies. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2021

Efgartigimod (Vyvgart™)

Goal(s):
- Restrict use to OHP-funded conditions.
- Promote use that is consistent with medical evidence.

Length of Authorization:
Up to 12 months

Requires PA:
- Vyvgart™ (efgartigimod) pharmacy and physician administered claims.

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the request for efgartigimod made by, or in consultation with, a neurologist or rheumatologist?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have an active infection?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7

Approval Criteria		
7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically included hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella. Immunization with live-attenuated or live vaccines is not recommended during efgartigimod treatment.	**Yes:** Go to #8. Document physician attestation of immunization history	**No:** Pass to RPh. Deny; medical appropriateness. Administer vaccines before initiation of a new treatment cycle of efgartigimod
8. Does the patient have a positive serological test for anti-AChR antibodies?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III or IV?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have a myasthenia gravis-specific activities of daily living scale (MG-ADL) total score of 6.5 points or more?	**Yes:** Go to #11 Record baseline MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient received or is currently receiving two immunosuppressant therapies (as monotherapy or in combination) for at least one year without adequate symptom control or do they have contraindications to these therapies? Example immunosuppressant therapies: - Azathioprine - Cyclosporine - Mycophenolate mofetil - Tacrolimus - Methotrexate - Cyclophosphamide	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of immunosuppressant therapy

Approval Criteria		
12. Is the request for efgartigimod dosing that corresponds to FDA labeling? • 10 mg/kg once weekly for 4 weeks • For patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion	**Yes:** Approve for up to two cycles. Each cycle is 1 dose/week for 4 weeks. The second cycle should not be administered sooner than 50 days from start of previous cycle.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/22 (KS)
Implementation:

Renewal Criteria		
1. Has it been 50 days or more from the start of the previous efgartigimod treatment cycle?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is this request for the first renewal of efgartigimod?	**Yes**: Go to #3	**No:** Go to #4
3. Has the patient experienced a reduction in symptoms of at least 2 points from MG-ADL total baseline score?	**Yes**: Approve for up to 5 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Has the patient maintained a stable MG-ADL score over the last 12 months of efgartigimod therapy?	**Yes**: Approve for up to 7 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

Drug Use Research & Management Program
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Drug Class Update: Fluoroquinolones, oral

Date of Review: April 2022

Date of Last Review: May 2018
Dates of Literature Search: 12/30/2017 – 12/07/2021

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

Purpose for Class Update:
The purpose of this class update is to review new comparative evidence for efficacy and safety of oral fluoroquinolone (FQ) antibiotics.

Research Questions:
1. Is there new comparative evidence that oral FQs differ in efficacy/effectiveness in the clinical cure of acute bacterial infections?
2. Is there new comparative evidence that oral FQs differ in serious adverse events or tolerability when used to manage acute bacterial infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which one oral FQ is more effective or associated with fewer adverse events?

Conclusions:
- Since the last class review, the Canadian Agency for Drugs and Technologies and Health (CADTH) published 5 systematic reviews focused on the efficacy of FQs for specific infections.[1-5] One systematic review focused on safety of FQs was published,[6] and 4 high-quality guidelines[7-10] were updated.

Systematic Reviews Focused on Efficacy
- No evidence was identified in 2019 by CADTH on the clinical effectiveness of FQs to treat otitis media in patients unable to take beta-lactam antibiotics.[1] Furthermore, no guidelines were found for the use of FQs for treatment of otitis media in patients unable to take beta-lactam antibiotics.[1]
- A 2019 CADTH report reviewed evidence for the use of FQs in intra-abdominal infections. The evidence suggests FQs do not differ from comparators (e.g. beta-lactams, ertapenem, ceftriaxone with metronidazole) with respect to effectiveness and safety for the treatment of adults with intra-abdominal infections.[2] The 2017 United States (U.S.) Surgical Infection Society (SIS) guideline recommends intravenous (IV) moxifloxacin or ciprofloxacin plus metronidazole for the empiric treatment of adults with lower-risk infection, with caution advised for those in regions with a high incidence of FQ-resistant *E. coli* (strong recommendation; high-quality evidence).[11] For pediatric patients, the SIS does not recommend moxifloxacin for empiric treatment unless other options are not available (strong recommendation; low-quality evidence).[11]

- A May 2019 CADTH report examined evidence for FQ use in patients with pneumonia.[3] Among patients with severe community acquired pneumonia (CAP), beta-lactam/macrolide combination therapy may be more effective than beta-lactam/FQ combination therapy in reducing overall mortality and length of hospital stay.[3] The 2014 National Institute for Health and Care Excellence (NICE) and 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidance recommend that FQs not be routinely offered for low-severity CAP,[12] and for ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP),[13] levofloxacin should be considered as an approach to cover methicillin-susceptible *S. aureus* (MSSA).
- A 2019 CADTH report evaluated FQs for the treatment of other respiratory infections.[4] Moxifloxacin showed an efficacy (defined as clinical cure rates at test-of-cure visit) close to or above 90% in patients with rhinosinusitis.[4] Levofloxacin showed an efficacy (clinical success, resolution of 3 or more acute rhinosinusitis symptoms) over 86%, although one study reported an efficacy of only 23.4% in patients with rhionsinusitis.[4] No significant differences in total pathogen eradication were noted between FQs, macrolides, or beta-lactams in a meta-analysis of patients with bronchitis.[4] In addition, 3 high-quality guidelines were identified; one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from NICE,[14] one informing the treatment of bronchiectasis in adults from the British Thoracic Society (BTS),[15] and one informing the treatment of chronic suppurative lung disease (CSLD) and bronchiectasis from the Thoracic Society of Australia and New Zealand.[16] The NICE guidance recommends levofloxacin for adults and ciprofloxacin (on specialist advice) for children as second-line oral treatments for patients at high risk of treatment failure or as first-line IV treatment.[14]
- An April 2019 CADTH report focused on the effectiveness of FQs for the treatment of urinary tract infections (UTI).[5] Three separate systematic reviews included patients with acute pyelonephritis, women with cystitis, and patients who experienced antibiotic-associated psychosis during treatment of a UTI.[5] In patients with pyelonephritis, the clinical success rates were not statistically different between cefaclor, ciprofloxacin, and norfloxacin at weeks 4 to 6.[5] Fluoroquinolones were effective for clinical and microbiological outcomes in patients with cystitis, but it was advised that they should be reserved for more invasive infections in order to avoid inducing bacterial resistance.[5] In terms of adverse events, there were cases of acute psychosis reported among patients treated with FQs, penicillins, or TMP-SMX for UTI.[5] 2018 NICE guidance recommends ciprofloxacin for pyelonephritis for non-pregnant women and men aged 16 years and over.[17] Fluoroquinolones are not recommended as first- or second-line therapy for catheter-associated UTI or lower UTI by NICE.[18,19] In the European Association of Urology (EAU) guideline, FQs are not recommended for uncomplicated cystitis.[20] For recurrent UTIs, there are conflicting recommendations between guidelines. NICE does not recommend FQs for recurrent UTIs.[21] However, the Society of Obstetricians and Gynecologists of Canada recommend daily prophylaxis with an FQ for women with 2 recurrent UTIs in 6 months or 3 recurrent UTIs in 12 months.[22]

Systematic Review Focused on Safety

- A 2021 systematic review investigated the association of FQ treatment and the risks of aortic aneurysm (AA) and aortic dissection (AD).[6] The pooled results of 9 studies showed that the use of FQs increased the risk of AA/AD by 69% (risk ratio [RR] 1.69; 95% CI, 1.08 to 2.64).[6] Stratified by the comparators, the use of FQs was associated with a higher risk of AA/AD compared to azithromycin (pooled RR 2.31; 95% CI 1.54 to 1.47) and amoxicillin (pooled RR 1.57; 95% CI 1.39 to 1.78).[6] In contrast, FQs were not associated with a higher risk of AA/AD, when compared with amoxicillin-clavulanate or ampicillin-sulbactam (pooled RR 1.18; 95% CI 0.81 to 1.73), and TMP-SMX (pooled RR 0.89; 95% CI 0.65 to 1.22).[6] Since FQs had a similar risk of AA/AD compared to some other broad-spectrum antibiotics, it is possible the risk of AA/AD could be related to the underlying severity of disease but not the antibiotics themselves.[6] Further prospective studies are warranted to clarify the role of FQs in the development of AA/AD after adjustment for underlying infection and its severity.[6]

Clinical Practice Guidelines

- In 2019, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) updated clinical practice guidance on the management of adults patients with CAP.[8] Respiratory FQs (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) are recommended for outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia (strong recommendation, moderate quality of evidence).[8]
- In 2019 the ATS, Centers for Disease Control and Prevention (CDC), European Respiratory Society (ERS), and IDSA jointly sponsored a new practice guideline on the treatment of multidrug-resistant tuberculosis (MDR-TB).[7] One of the specific questions selected by the guideline writing committee addressed if

outcomes are safely improved in patients with MDR-TB when regimens include FQs compared with regimens that do not include FQs.[7] The guideline recommends including moxifloxacin or levofloxacin in a regimen for treatment of patients with MDR-TB (strong recommendation, low certainty in the evidence).[7]

- In September 2019, NICE updated guidance focused on antibiotic prescribing to treat CAP in adults and children.[9] Levofloxacin is only recommended as an alternative antibiotic for adults with high-severity CAP and a penicillin allergy.[9] For children under 18 years of age, FQs are not recommended for treatment of any forms of CAP.[9]
- The NICE guidance focused on antimicrobial stewardship was updated in 2019.[10] A section on FQ safety was added due to the numerous safety issues associated with FQ administration. Fluoroquinolones should not be used: 1) to treat self-limiting infections, or infections that are not severe; 2) to treat non-bacterial conditions or 3) to treat some mild to moderate infections (such as acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease), unless other antibiotics that are commonly recommended for these infections are not appropriate.[10]

Specific Subgroup Analysis

- No evidence was identified for subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities to demonstrate one oral FQ is more effective or associated with fewer adverse events over other FQs.

Expanded Indication

- Delafloxacin (BAXDELA) received expanded FDA-approval to treat adults with CAP.[23] When delafloxacin was initially approved in 2018, it was indicated for treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. For the expanded indication, delafloxacin was evaluated in a single, noninferiority, multicenter, multinational, randomized, double-blind trial in adults with CAP (n = 859).[24] The primary end point was early clinical response, defined as improvement at 96 (± 24) hours after the first dose of study drug.[24] In the intent-to-treat (ITT) analysis population, ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group (difference -0.2%; 95% CI -4.4% to 4.1%).[24] In this RCT, noninferiority of delafloxacin was demonstrated compared with moxifloxacin for treatment of CAP.[24]

Recommendations:

- Based on the review of recently published evidence, recommend adding moxifloxacin as a preferred agent to the Preferred Drug List (PDL).
- Review drug costs in Executive Session.

Summary of Prior Reviews and Current Policy

Evidence for the comparative effectiveness of FQs was last reviewed by the Oregon Pharmacy and Therapeutic (P&T) Committee in May 2018. The efficacy and safety of delafloxacin, which received Food and Drug Administration (FDA) approval in 2017 for treatment of adults with ABSSSI, was also reviewed at this meeting. The oral FQs included on the Oregon PDL are presented in **Appendix 1.** Ciprofloxacin and levofloxacin are preferred agents on the PDL in order to maintain at least one FQ with broad coverage of gram-negative bacteria and at least one "respiratory" FQ as preferred options. In the third quarter of 2021, all of the Fee-For-Service oral FQ utilization was for ciprofloxacin and levofloxacin.

Background:

Discovery of quinolone antibiotic prototype, nalidixic acid, occurred during the synthesis of the antimalarial agent, chloroquine in the early 1960s.[25] Nalidixic acid never became a useful agent to treat systemic infections because of its narrow antibacterial spectrum, poor tissue penetrability, rapid emergence of bacterial resistance, and frequent adverse central nervous system (CNS) effects.[25] However, nalidixic acid did provide the chemical foundation upon which to build the modifications that would subsequently improve therapeutic properties and limit adverse effects of the quinolone antibiotics.[25] In rapid succession, norfloxacin,

ciprofloxacin, and levofloxacin were discovered, developed, and licensed for use.[26] The FQs are strong inhibitors of topoisomerase II (DNA gyrase) and topoisomerase IV, which interfere with bacterial DNA synthesis.[27] Fluoroquinolones are bactericidal and exhibit post-antibiotic effects of inhibition of bacterial growth even after the plasma concentration falls below the minimum inhibitory concentration (MIC).[27]

Fluoroquinolones have good oral bioavailability and penetrate most body tissues. Other than moxifloxacin, the FQs are eliminated through the kidneys via active tubular secretion.[28] Fluoroquinolones have a broad spectrum of activity against gram-negative and gram-positive bacteria. They are used in the treatment of genitourinary infections, prostatitis, respiratory diseases, sexually transmitted diseases, gastroenteritis, and skin/soft tissue infections. The Food and Drug Administration (FDA)-approved indications for oral FQs are presented in **Table 1** for adults and **Table 2** for children. Due to the broad-spectrum activity of FQs, there is widespread incentive to preserve the efficacy of these drugs by reserving them as second-line when narrow-spectrum antibiotics can be utilized first. Resistance to FQs is also increasing rapidly and is considered a major concern in the clinical setting.[29] Because resistance to FQs is common, knowledge of local epidemiology is important when selecting an antibiotic.[29]

Table 1. FDA-Approved Indications for Oral Fluoroquinolones in Adults with Normal Renal Function (CrCl > 50 mL/min)

Infection	Ciprofloxacin[30]	Ofloxacin[31]	Levofloxacin[32]	Moxifloxacin[33]	Delafloxacin[23]
Skin and Skin Structure	X	X	X	X	X
Bone and Joint	X				
Complicated Intra-abdominal	X			X	
Infectious Diarrhea	X				
Typhoid Fever	X				
Uncomplicated Urethral and Cervical Gonorrhea	X	X			
Inhalational Anthrax (post-exposure)	X		X		
Plague	X		X	X	
Nosocomial Pneumonia			X		
Community Acquired Pneumonia	X	X	X	X	X
Acute Exacerbation of Chronic Bronchitis	X	X	X	X	
Chronic Bacterial Prostatitis	X	X	X		
Uncomplicated Urinary Tract	X	X	X		
Complicated Urinary Tract or Acute Pyelonephritis	X		X		
Uncomplicated Cystitis	X	X			
Acute Pelvic Inflammatory Disease		X			
Acute Bacterial Sinusitis	X		X	X	
Abbreviations: CrCl=creatinine clearance FDA=Food and Drug Administration; mL=milliliters; min=minute					

Table 2. FDA-Approved Uses and Dosing Of Oral Fluoroquinolones in Pediatric Patients with Normal Renal Function (CrCl > 50mL/min)

Infection	Ciprofloxacin[30]	Levofloxacin[32]
Inhalational Anthrax (post-exposure)	X*	X
Plague	X*	X
Complicated Urinary Tract or Acute Pyelonephritis	X**	

**approved in patients from birth to 17 years of age*
***approved in patients from 1 to 17 years of age*
Abbreviations: CrCl=creatinine clearance FDA=Food and Drug Administration; mL=milliliters; min=minute

Fluoroquinolones are associated with serious AEs affecting the CNS, musculoskeletal, and peripheral nervous systems,[34] with more recent evidence of aortic aneurysm and aortic dissection.[35] Fluoroquinolones have also been associated with both hypoglycemia and hyperglycemia in diabetic and nondiabetic patients.[36,37] The incidence of *C. difficile* infection also appears to be higher with FQ use when compared with some other antibiotics.[38] Fluoroquinolones should generally be avoided during pregnancy and lactation unless a safer alternative is not available.[39] In animal models, FQ use during pregnancy has been associated with cartilage and bone toxicity in developing fetuses.[39] Routine use of FQs in children should be limited to the treatment of infections for which no safe and effective alternative exists due to the potential risk of musculoskeletal toxicity.[40,41] All FQs marketed in the United States (U.S.) contain a black boxed warning regarding the risk of serious AEs including tendinitis, tendon rupture, peripheral neuropathy, CNS effects, and exacerbation of myasthenia gravis.[23,30-33] With these warnings, the FDA stated the benefit for use of FQs for acute sinusitis, acute bronchitis, and uncomplicated UTIs, does not outweigh risks of serious AEs and use in these indications should be reserved for those patients who lack any alternative treatment options.[42] Notably, several FQs have been withdrawn from the market due to AEs; for instance, grepafloxacin was withdrawn from the worldwide market in 1999 due to seven fatal cardiovascular events; trovafloxacin was withdrawn from European and U.S. markets in 1999 due to reports of liver failure; gatifloxacin was removed from the market in 2006 following a study published on dysglycemia side effects; temafloxacin was withdrawn from the American and some European markets shortly following its approval in 1992 due to severe adverse reactions, including hemolytic anemia, acute renal failure, hepatotoxicity and 3 deaths; sparfloxacin was withdrawn from American markets in 2001 due to QT prolongation and photoxicity; and alatrofloxacin was withdrawn worldwide in 2006 due to associations with liver toxicity and death.[3]

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

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

New Systematic Reviews:
In 2019 the Canadian Agency for Drugs and Technologies and Health (CADTH) published 5 reports focused on the safety and efficacy of FQs for different infections including otitis media, intra-abdominal infections, pneumonia, other respiratory infections, and UTIs. No evidence regarding the clinical effectiveness of FQs to treat otitis media in patients unable to take beta-lactam antibiotics was identified by the CADTH reviewers.[1] Furthermore, no guidelines regarding the use of FQs for the treatment of otitis media in patients unable to take beta-lactam antibiotics were found.[1] CADTH reports for the use of FQs in the treatment of intra-abdominal, respiratory, and urinary tract infections supported by moderate- to high-quality evidence are summarized below.

Fluoroquinolones for Intra-Abdominal Infections
An April 2019 CADTH report evaluated the evidence for the use of FQs in the treatment of intra-abdominal infections.[2] Due to the development of resistance over time in some locations and the potential for severe adverse effects, decisions around the prescription of FQs for the treatment of intra-abdominal infections and the choice of a FQ regimen should consider local and regional susceptibility information, whether infections are hospital-, intensive care unit-, or community-associated, and the benefits and harms associated with their use.[2] One systematic review with meta-analysis, one meta-analysis without systematic review, 2 RCTs, and one evidence-based guideline met inclusion criteria for the CADTH report.[2] Intervention and comparator treatments were initiated intravenously, with the possibility to switch to oral treatment once the patient became stable.[2]

In the moderate-quality 2019 systematic review (n = 4,125), FQ-based regimens did not differ in efficacy from beta-lactam-based regimens for the treatment of complicated intra-abdominal infections in adults (RR 0.97; 95% CI 0.94 to 1.01).[2] In the moderate-quality, 2014 meta-analysis (n = 1,229), the authors concluded moxifloxacin had similar efficacy compared to 4 antibiotic regimens (piperacillin-tazobactam followed by amoxicillin-clavulanate; ceftriaxone plus metronidazole, followed by amoxicillin-clavulanate; ceftriaxone plus metronidazole; or ertapenem) for the treatment of complicated intra-abdominal infections in adults (pooled difference in success rates -3.96; 95% CI -7.06 to -1.05; P = 0.25).[2] A 2018 low-quality RCT of pediatric patients (n = 451) treated for complicated intra-abdominal infection, showed the moxifloxacin group experienced greater treatment success and clinical cure compared with ertapenem followed by amoxicillin-clavulanate, although statistical significance was not assessed.[2] In a 2017 low-quality RCT of adult patients with peritoneal dialysis related peritonitis (n = 80), there were no statistically significant differences in complete cure, primary treatment failure, secondary treatment failure, peritonitis-related death, successive episodes of peritonitis up to 3 months follow-up, successive episodes of peritonitis, transfer to hemodialysis, or maintenance of peritoneal dialysis between oral moxifloxacin and intraperitoneal ceftazidime.[2]

In a systematic review of patients with complicated intra-abdominal infection, FQ-based regimens did not differ from beta-lactam-based regimens with regard to all-cause mortality (RR 1.04; 95% CI 0.75 to 1.43), overall treatment-related AEs (RR 0.97; 95% CI 0.70 to 1.33), or early study withdrawal due to AEs (RR 1.07; 95% CI 0.86 to 1.33).[2] In the meta-analysis without systematic review that examined moxifloxacin for the treatment of complicated intra-abdominal infections, the rates of AEs were similar to the 4 comparator groups for overall AEs (67.3% vs 59.8%), drug-related AEs occurring in more than 5 patients in either group (20.9% vs. 20%), serious AEs (18.1% vs. 14.2%), premature discontinuations due to AEs (5.1% vs. 4.0%), and deaths (4.3% vs. 3.4%).[2] In the pediatric RCT, the investigators determined the rates of FQ AEs were similar to the ertapenem followed by amoxicillin-clavulanate group for all AEs, with the exception of QT prolongation.[2] In the adult RCT, there were greater occurrences of QT prolongation assessed by electrocardiogram (ECG) in the moxifloxacin group versus ceftazidime.[2] However, statistical significance was not examined for AE outcomes in either RCT.[2]

The 2017 SIS guideline provides recommendations on the use of FQs in the treatment of community-acquired intra-abdominal infections for adults and pediatric patients.[11] This high-quality guideline used rigorous methodology and provided support for implementation of recommendations.[2] For adults, IV moxifloxacin or the combination of ciprofloxacin plus metronidazole are recommended for the empiric treatment of those with lower-risk infection, with caution advised for

those in regions with a high incidence of FQ-resistant *E. coli* (strong recommendation; high-quality evidence).[11] Levofloxacin plus metronidazole is recommended where other FQs are unavailable (weak recommendation, low-quality evidence).[11] Fluoroquinolone-based regimens in general are recommended for initial empiric antimicrobial therapy in lower risk patients who have had major reactions to beta-lactams (weak recommendation; moderate-quality evidence).[11] For pediatric patients, the SIS does not recommend moxifloxacin for empiric treatment unless other options are not available (strong recommendation; low-quality evidence).[11] Ciprofloxacin plus metronidazole (weak recommendation, moderate-quality evidence) or levofloxacin (weak recommendation, low-quality evidence) are recommended for empiric treatment of children older than 1 month if other options are not suitable, particularly for children who have had life-threatening reactions to beta-lactam (weak recommendation, moderate-quality evidence).[11] The SIS recommends against empiric use of most FQ-based regimens in residents of geographic areas where a high prevalence of extended spectrum beta-lactamase-producing *Enterobacteriaceae* exists in the community (strong recommendation; moderate-quality evidence).[11]

In summary, evidence from 2 moderate-quality systematic reviews, and 2 low-quality RCTs suggests FQs do not differ from comparators with respect to effectiveness and safety for the treatment of adults with intra-abdominal infections.[2] The 2017 SIS guideline provides recommendations for use of specific FQs in adults and children with community acquired intra-abdominal infections.[2] Key limitations were identified by authors of the CADTH report. There was limited or no evidence available on the effectiveness and safety of FQs for some populations of interest.[2] Pediatric patients were only examined in one small, pilot study and statistical significance was not calculated.[2] Complicated intra-abdominal infections and secondary peritonitis were examined but other uncomplicated types of intra-abdominal infection were not examined in clinical studies.[2] Finally, given that susceptibility to antibiotic resistance differs across regions, it is unclear if the included studies would be generalizable to specific geographic regions.[2]

Fluoroquinolones for the Treatment of Pneumonia

A May 2019 CADTH report identified 9 moderate-quality systematic reviews and 2 high-quality guidelines which examined evidence for FQ use in patients with pneumonia.[3] The 9 systematic reviews describing patients with pneumonia identified various antibiotic regimens including: FQ versus either a macrolide or doxycycline, in combination with a beta-lactam; beta-lactam plus macrolide combination versus beta-lactam plus FQ combination; FQ monotherapy versus macrolide monotherapy; or ceftriaxone plus macrolide combination therapy versus FQ monotherapy.[3] The CADTH authors noted potential limitations in findings due to a high risk of bias among the studies included in the systematic reviews.[3] The generalizability of the findings is limited by variability of included study design, interventions, and comparators.[3] Findings from 3 systematic reviews suggested that alternative antibiotic regimens may be more effective in reducing mortality compared to FQ-containing regimens.[3] Among patients with severe community acquired pneumonia (CAP), beta-lactam plus macrolide combination therapy may be more effective than beta-lactam plus FQ combination therapy in reducing overall mortality (overall mortality rates were 19.4% versus 26.8%, respectively; OR 0.68; 95% CI 0.49 to 0.94; P = 0.02) and length of hospital stay (MD −3.05 days; 95% CI −6.01 to −0.09; P = 0.04).[3] The remaining systematic reviews describing patients with pneumonia examined the efficacy of antibiotics using clinical cure or clinical failure as the primary outcome.[3] One study reported that treatment with FQ monotherapy resulted in lower clinical failure than treatment with beta-lactam monotherapy (RR 0.72; 95% CI 0.57 to 0.91).[3] A meta-analysis showed no statistically significant difference in treatment success between ceftriaxone combination therapy and respiratory FQ monotherapy (pooled RR 0.96; 95% CI 0.92 to 1.01).[3] Drug-related adverse events were found to be significantly lower with ceftriaxone combination therapy than respiratory FQ monotherapy (pooled RR 1.27; 95% CI 1.04 to 1.55).[3]

The two guidelines cited low quality evidence as a consideration when implementing their recommendations.[3] The 2014 NICE guidance is intended to be relevant to the management of most patients with CAP or HAP.[12] The 2016 clinical practice guidelines by the IDSA/ATS is intended for use by the healthcare professionals who care for patients at risk for HAP and VAP.[13] It is recommended that for low-severity CAP, FQs should not routinely be offered,[12] and for VAP and HAP,[13] levofloxacin should be considered as an approach to cover MSSA.

Fluoroquinolones for the Treatment of Other Respiratory Tract Infections

Five publications met the eligibility criteria and were included in a 2019 CADTH report which evaluated FQs in the treatment of other respiratory infections.[4] Two of the included publications were moderate-quality systematic reviews; one systematic review which examined antibiotic use in patients with acute rhinosinusitis, and one systematic review with a meta-analysis and a network meta-analysis which examined anti-bacterial agents for patients with bronchitis.[4] In addition, 3 high-quality guidelines were identified; one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from NICE,[14] one informing the treatment of bronchiectasis in adults from the BTS,[15] and one informing the treatment of CSLD and bronchiectasis from the Thoracic Society of Australia and New Zealand.[16]

In the systematic review of the treatment of acute rhinosinusitis, 6 studies assessed the efficacy of levofloxacin and 5 studies evaluated moxifloxacin; however, the route of administration (e.g. oral, inhaled, IV) was not reported.[4] The primary outcome was clinical cure rate (based on symptoms, and signs detected in physical and/or endoscopic exam) at 5 or 10 days.[4] Six RCTs of levofloxacin reported efficacy (clinical success, resolution of 3 or more acute rhinosinusitis symptoms) over 86% (median efficacy 91.4%, range: 23.4 to 93.9%), although one study reported an efficacy of only 23.4%.[4] Four of the RCTs of levofloxacin showed occurrence of minor AE to be less than 22.5%, although two RCTs showed it to be around 40%; no major AEs were reported.[4] For moxifloxacin, the majority of the included RCTs demonstrated efficacy (defined as clinical cure rates at test-of-cure visit) close to or above 90% (median efficacy 86%, range: not reported).[4] The minor AE profile of moxifloxacin ranged from 24.3% to 38.2% and no major AEs were observed.[4] The authors noted that with the exception of one RCT, levofloxacin was shown to be the most effective FQ for treatment of acute rhinosinusitis.[4]

The systematic review focused on treatment of bronchitis based on evidence from 27 RCTs.[4] The FQs and comparators in the RCTs included: levofloxacin versus amoxicillin-clavulanate; moxifloxacin versus amoxicillin-clavulanate; gemifloxacin versus amoxicillin-clavulanate; gatifloxacin versus amoxicillin-clavulanate; levofloxacin versus azithromycin; moxifloxacin versus azithromycin; gemifloxacin versus clarithromycin; moxifloxacin versus clarithromycin; gatifloxacin versus clarithromycin; and levofloxacin versus gemifloxacin.[4] Of note, gatifloxacin and gemifloxacin are no longer marketed in the U.S. The route of treatment (e.g. oral or IV) and the length of follow-up was not reported for any RCTs.[4] The main outcomes were total pathogen eradications and the total incidence of adverse events.[4] No significant differences across the included medications in treatment efficacy for total pathogen eradication were noted in the meta-analysis.[4] However, the results showed that patients treated with gemifloxacin had a lower risk of adverse events when compared to patients treated with amoxicillin-clavulanate (OR = 0.58, 95% CI 0.36 to 0.91).[4] Furthermore, patients treated with FQs compared to amoxicillin-clavulanate had a reduced risk of diarrhea, including moxifloxacin (OR 0.39, 95% CI 0.18 to 0.82), gemifloxacin (OR 0.22, 95% CI 0.09 to 0.50) and gatifloxacin (OR 0.31, 95% CI 0.13 to 0.85). This reduction was also observed among patients treated with levofloxacin compared to those treated with azithromycin (OR 0.41, 95% CI 0.17 to 0.96).[4] For the FQs, the authors reported that gemifloxacin and levofloxacin had a relatively high ranking in total pathogen eradication efficacy.[4] Though moxifloxacin revealed good performance in total pathogen eradication and pathogen eradication of *H. influenzae*, it was accompanied with a poor performance in pathogen eradication of *S. pneumonia*.[4]

The BTS guideline was developed for healthcare practitioners who are involved in the care of adult patients with bronchiectasis (e.g. primary care clinicians, hospital teams in infectious disease, respiratory medicine, microbiologists, and radiologists).[4] The NICE guideline is intended for health professionals as well as people with bronchiectasis, their families and caregivers.[4] The Thoracic Society of Australia and New Zealand guideline is intended for the management of children and adults in Australia and New Zealand with CSLD and bronchiectasis, including urban and rural-remote indigenous people.[4] The BTS and the Thoracic Society of Australia and New Zealand guideline recommend ciprofloxacin as a first-line treatment for patients with *P. aeruginosa*.[15,16] The NICE guidance recommends levofloxacin for adults and ciprofloxacin (on specialist advice) for children as second-line oral treatments for patients at high risk of treatment failure or as first-line IV treatment.[14] While the 3 guidelines provide similar recommendations for the use of FQs in the treatment of bronchiectasis, the variable

findings and methodological limitations in the body of evidence identified for other conditions, including bronchitis and acute rhinosinusitis, limit generalizability and warrant caution in its interpretation for the clinical effectiveness and cost-effectiveness of FQs for the treatment of respiratory tract infections other than pneumonia.[4]

Fluoroquinolones for the Treatment of Urinary Tract Infection

An April 2019 CADTH report focused on the effectiveness of FQs for the treatment of UTIs.[5] Evidence was identified for the following FQs: ciprofloxacin, gatifloxacin, levofloxacin, norfloxacin, and ofloxacin.[5] Three low-quality systematic reviews, 9 high-quality RCTs, 1 moderate-quality RCT, 6 moderate-quality, non-randomized studies, and 6 high-quality guidelines met inclusion criteria.[5] The outcomes considered in the systematic reviews were clinical success in the treatment of acute pyelonephritis, symptom cure, symptom resolution, recurrence of cystitis, treatment duration, and AEs.[5] In the RCTs, the outcomes were clinical success rates, microbiological eradication, microbiological recurrence, clinical relapse, early response, susceptibilities of pathogens, cure rates, symptom-free cure, clinical effectiveness rates, treatment failure, composite cure, and AEs.[5]

The 3 systematic reviews included patients with acute pyelonephritis, women with cystitis, and patients with antibiotic-associated psychosis.[5] Fluoroquinolones were compared with other antibiotics (trimethoprim-sulfamethoxazole [TMP-SMX], loracarbef, nitrofurantoin, fosfomycin, beta-lactams, and metronidazole) or with another FQ in the review focused on pyleonephritis.[5] The clinical success rates were not statistically different between cefaclor, ciprofloxacin, and norfloxacin at weeks 4 to 6.[5] Relatively high rates of AEs were observed in one trial of ciprofloxacin (24%) and TMP-SMX (33%) compared to the incidence of AEs in other RCTs.[5] In another systematic review focused on adult women with uncomplicated cystitis, FQs were compared to TMP-SMX, nitrofurantoin, or fosfomycin.[5] Fluoroquinolones were effective for clinical and microbiological outcomes, but it was advised that they should be reserved for more invasive infections in order to avoid inducing bacterial resistance.[5] The authors concluded that options of antibiotics for women with diabetes without voiding abnormalities were similar to those for women without diabetes.[5] In the third systematic review, a systematic search was conducted for cases of acute psychosis that occurred during UTI treatment.[5] Acute psychosis was considered a potential AE of antibiotic treatment of UTIs, although the mechanism remained unknown. Three classes of antibiotics were implicated: FQs, penicillins, and TMP-SMX.[5]

The RCTs revealed different FQ efficacy rates depending upon the active comparator and severity of the UTI.[5] Patients with acute pyelonephritis, complicated UTIs, uncomplicated UTIs, or acute obstructive pyelonephritis were recruited for the 10 RCTs.[5] In the RCTs, the FQs included: levofloxacin, ciprofloxacin, and norfloxacin. The FQs were compared with ceftriaxone, ertapenem, ceftazidime, TMP-SMX, or ceftolozane-tazobactam. Among patients with acute obstructive pyelonephritis, ceftazidime was associated with significantly higher clinical or microbiological cure rates than ciprofloxacin after drainage, percutaneous nephrostomy or urethral stenting.[5] Compared to TMP-SMX, levofloxacin and norfloxacin did not statistically differ for the treatment of uncomplicated UTIs based on bacterial cure rates.[5] Compared to levofloxacin, the combination of ceftolozane and tazobactam was associated with statistically significantly better responses in a composite of microbiological eradication and clinical cure in patients with complicated lower UTIs or pyelonephritis.[5]

There were 2 RCTs in which different routes or treatment durations of FQs were compared. The first compared a short-course (5-day) of IV levofloxacin to the conventional combination of IV and oral levofloxacin regimen (i.e. total of 7 to 14 days of IV and oral treatment), which were similarly effective in clinical and microbiological efficacy, tolerance, and safety among patients with complicated UTIs or acute pyelonephritis.[5] From a clinician perspective, the short-course regimen was a more convenient alternative.[5] The need for antimicrobial treatment was not significantly different between patients treated with a 10-day IV ciprofloxacin regimen or a 5-day IV levofloxacin regimen among male patients with complicated UTIs.[5] In patients with acute uncomplicated pyelonephritis, clinical and microbiological cure were not statistically different between those treated with 5- or 10-days of ofloxacin or levofloxacin.[5]

In the non-randomized studies, elderly patients with suspected UTIs, UTIs and a positive urine culture, *E. coli* pyelonephritis, community-acquired complicated UTIs, or a diagnosis of UTI were studied.[5] Treatment with FQs (i.e., ciprofloxacin, levofloxacin, norfloxacin, or ofloxacin) was compared to treatment with the following antibiotics: cephalexin, amoxicillin-clavulanate, nitrofurantoin, piperacillin-tazobactam, gentamicin, cefuroxime, cefpodoxime, ceftazidime, TMP-SMX, ceftriaxone, ertapenem, first-generation cephalosporins (including cefazolin or cephalexin), penicillins (ampicillin-sulbactam, amoxicillin-clavulanate, or piperacillin-tazobactam), nitrofurantoin, or fosfomycin.[5] Compared with nitrofurantoin, the use of ciprofloxacin, cephalexin, or amoxicillin-clavulanate was associated with lower rates of treatment failure, defined by re-consultation and re-prescription, in older people with UTIs.[5] The risks of UTI-related hospitalization or death did not statistically differ between patients treated with nitrofurantoin and those treated with ciprofloxacin, cephalexin, or amoxicillin-clavulanate.[5] When ciprofloxacin, piperacillin-tazobactam, gentamicin, cefuroxime, cefpodoxime, and ceftazidime were compared to each other, cephalosporins were the best choice based on antibiotic resistance for UTI patients without any risk factors.[5] Compared to ciprofloxacin, 7-day TMP-SMX treatment was similarly effective for pyelonephritis based on the occurrence of subsequent symptomatic UTIs.[5] In patients with UTIs using warfarin, the authors of a non-randomized study concluded that ciprofloxacin, first-generation cephalosporins, and penicillins were preferred because of significantly less drug-drug interactions with warfarin compared to ceftriaxone, which was associated with significantly higher peak international normalized ratio (INR) readings, significantly greater change in INR, and significantly greater percentage change in INR.[5] Patients with UTIs treated with norfloxacin or ofloxacin there were statistically significantly lower composite treatment failure rates compared to patients treated with ciprofloxacin or TMP-SMX.[5]

The 2018 SOGC,[22] 2019 EAU,[20] and 2018 NICE guidelines provide recommendations for the use of FQs for different UTI categories. Guidance from NICE is published in 4 separate documents focused on: 1) catheter-associated UTIs,[18] 2) pyleonephritis,[17] 3) lower urinary tract infections,[19] and 4) recurrent UTIs.[21] The NICE guidance for pyelonephritis recommends ciprofloxacin for non-pregnant women and men aged 16 years and over.[17] In NICE guidance, FQs are not recommended as first- or second-line therapy for catheter-associated UTIs[18] or lower UTIs.[19] For recurrent UTIs, FQs are not recommended.[21] In the EAU guidance, ciprofloxacin, levofloxacin, and ofloxacin are not recommended in uncomplicated cystitis (strong evidence).[20] Ciprofloxacin and levofloxacin are recommended for initial empirical oral therapy in uncomplicated pyelonephritis (no evidence level).[20] Ciprofloxacin is recommended for complicated pyelonephritis in women if the local resistance pattern remains less than 10% and the patients have contraindications for third-generation cephalosporins or an aminoglycoside.[20] The EAU advises not to use FQs empirically in patients from urology departments or those exposed to FQs in the last 6 months.[20] In contrast, in the SOGC guidance, FQs are recommended as one of the antibiotics used for daily prophylaxis for women with two recurrent UTIs in 6 months or 3 recurrent UTIs in 12 months.[22]

Association between the Risk of Aortic Aneurysm/Aortic Dissection and the Use of Fluoroquinolones

A 2021 systematic review investigated the association of FQ treatment and the risks of aortic aneurysm and aortic dissection.[6] The literature search was conducted through February 2021. Nine case series and cohort studies met inclusion criteria.[6] Three studies each were conducted in Taiwan and the U.S., and one each in Canada, France and Sweden.[6] No RCTs were identified. All 9 observational studies had a low risk of bias according to study design, data collection and analyses.[6] The quality of the evidence for the outcome of aortic aneurysm/aortic dissection using grading of recommendations assessment, development and evaluation (GRADE) methodology was rated as moderate.[6]

The pooled results of 9 studies showed that the use of FQs increased the risk of aortic aneurysm/aortic dissection by 69% (RR 1.69; 95% CI 1.08 to 2.64; I^2 = 99.8%).[6] Similar results were found for aortic aneurysm (pooled RR 1.58; 95% CI 1.21 to 2.07; I^2 = 95.6%) but no significant association was observed for aortic dissection (pooled RR 1.23; 95% CI 0.93 to 1.62).[6] Stratified by the comparators, the use of FQs was associated with a higher risk of aortic aneurysm/aortic dissection compared to azithromycin (pooled RR 2.31; 95% CI 1.54 to 1.47) and amoxicillin (pooled RR 1.57; 95% CI 1.39 to 1.78).[6] In contrast, FQs were not associated with a higher risk of aortic aneurysm/aortic dissection when compared with amoxicillin-clavulanate or ampicillin-sulbactam (pooled RR 1.18; 95% CI

0.81 to 1.73), TMP-SMX (pooled RR 0.89; 95% CI 0.65 to 1.22) or other antibiotics (pooled RR 1.14; 95% CI 0.90 to 1.46).[6] Clinically, amoxicillin and azithromycin would be only prescribed for patients with mild infections, and FQs and other broad-spectrum antibiotics would be prescribed for patients with moderate or severe infections.[6] Although most of the findings in this meta-analysis suggest a possible association between the use of FQs and the development of aortic aneurysm/aortic dissection, there is still concern about the results because the included studies had high heterogeneity (most I^2 50% or greater) and the findings of the asymmetric funnel plot indicated possible publication bias.[6] Fluoroquinolones were associated with an increased risk of aortic aneurysm or aortic dissection, although the level of evidence was not robust.[6] However, compared with other broad-spectrum antibiotics (i.e. some beta-lactams, TMP-SMX), FQs had a similar risk of aortic aneurysm/aortic dissection, suggesting that the risk of aortic aneurysm/aortic dissection could be related to the underlying severity of disease but not antibiotics themselves.[6] Further prospective studies are warranted to clarify the role of FQs in the development of aortic aneurysm/aortic dissection after adjustment for underlying infection and its severity.[6]

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), [43-47] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

American Thoracic Society/Infectious Diseases Society of America: Management of Adults with Community-Acquired Pneumonia

In 2019, the ATS and IDSA updated clinical practice guidance on the management of adult patients with CAP.[8] A multidisciplinary panel conducted pragmatic systematic reviews of the relevant research and applied GRADE methodology for clinical recommendations.[8] Antibiotic recommendations for the empiric treatment of CAP were based on selecting agents effective against the major treatable bacterial causes of CAP.[8] Traditionally, these bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*.[8] The microbial etiology of CAP is changing, particularly with the widespread introduction of the pneumococcal conjugate vaccine, and there is increased recognition of the role of viral pathogens.[8] Recommendations focused on antibiotic selection and duration of therapy are summarized below.

- *In the Outpatient Setting, Which Antibiotics Are Recommended for Empiric Treatment of CAP in Adults?*
  1. For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia the following antibiotics are recommended (in no particular order of preference):
  - amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND
  - macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy); OR
  - respiratory FQ (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) (strong recommendation, moderate quality of evidence).[8]

- *In Outpatient and Inpatient Adults with CAP Who Are Improving, What Is the Appropriate Duration of Antibiotic Treatment?*
  - The duration of antibiotic therapy should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities [heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature], ability to eat, and normal mentation), and antibiotic therapy should be continued until the patient achieves stability and for no less than a total of 5 days (strong recommendation, moderate quality of evidence).[9]

American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America: Treatment of Multidrug-Resistant Tuberculosis

In 2019 the ATS, CDC, ERS, and IDSA jointly sponsored a new practice guideline on the treatment of MDR-TB.[7] A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pediatrics, primary care, public health, epidemiology, economics, pharmacokinetics, microbiology, systematic review methodology, and patient advocacy, was assembled to assess the evidence supporting each recommendation.[7] One of the specific questions selected by the guideline writing committee addressed if outcomes are safely improved in patients with MDR-TB when regimens include FQs compared with regimens that do not include FQs.[7] Ofloxacin, followed by levofloxacin, followed by moxifloxacin sequentially improved the earlier generation's spectrum of activity, including mycobacteria, and their antimycobacterial action increased as evidenced by lower minimum inhibitory concentrations (MICs) and increasing success in clinical use.[7] Physicians began using these drugs to treat MDR-TB on the basis of *in vitro* data, with subsequent case series and observational studies showing efficacy although none of the FQs are currently indicated by the FDA for the treatment of TB.[7] Among patients with susceptible isolates, levofloxacin-containing regimens compared with no FQ were associated with greater treatment success (adjusted OR 4.2; 95% CI 3.3 to 5.4) and fewer patient deaths (adjusted OR 0.6; 95% CI 0.5 to 0.7). Moxifloxacin, compared with a regiment that did not include a FQ, was also associated with greater treatment success (adjusted OR 3.8; 95% CI 2.8 to 5.2) and fewer patient deaths (adjusted OR 0.5; 95% CI 0.4 to 0.6).[7] In pairwise comparisons, both levofloxacin and moxifloxacin were associated with statistically significantly better treatment outcomes than ofloxacin.[7] The adjusted ORs of death were lower for the two later-generation FQs when compared with ofloxacin (levofloxacin: adjusted OR 0.8; 95% CI 0.6 to 0.9; moxifloxacin: adjusted OR 0.8; 95% CI 0.6 to 1.0).[7] Ofloxacin and ciprofloxacin are considered inferior FQs against *M. tuberculosis*.[7] Levofloxacin and moxifloxacin did not statistically differ from each other.[7]

The guideline recommends including moxifloxacin or levofloxacin in a regimen for treatment of patients with MDR-TB (strong recommendation, low certainty in the evidence).[7] The recommendation for the use of moxifloxacin or levofloxacin is strong despite very low certainty in the evidence because the panel viewed the statistically significant reduction in mortality, improved treatment success, and relatively AEs associated with MDR-TB treatment with FQ regimens.[7]

National Institute for Health and Care Excellence: Community-Acquired Pneumonia: Antimicrobial Prescribing

In September 2019, NICE updated guidance focused on antibiotic prescribing to treat CAP in adults and children.[9] For adults aged 18 years and over, a 5-day course of amoxicillin, doxycycline, or clarithromycin are recommended to treat mild, moderate, or severe CAP.[9] Erythromycin is recommended in pregnancy.[9] Levofloxacin is only recommended as an alternative antibiotic for adults with high-severity CAP and a penicillin allergy.[9] For children under 18 years of age, FQs are not recommended for treatment of any forms of CAP.[9] First choice oral antibiotic recommendations for treatment of CAP in children include amoxicillin or clarithromycin dosed according to age or weight.[9]

National Institute for Health and Care Excellence: Antimicrobial Stewardship

The NICE guidance focused on antimicrobial stewardship was updated in 2019.[10] A section on FQ safety was added due to the numerous safety issues associated with FQs. For example, in the November 2018 edition of the Drug Safety Update, the Medicines and Healthcare products Regulatory Agency (MHRA) highlighted a small increased risk of aortic aneurysm and dissection with systemic and inhaled FQs, and recommended caution and advice for prescribing in people with a high risk.[10] In the March 2019 edition of the Drug Safety Update, the MHRA highlighted new restrictions and precautions for use with the FQs following an European-Union-wide review into the safety of these antibiotics.[10] The review found that very rarely, people having treatment with these antibiotics by mouth, injection or inhalation reported long-lasting and disabling side effects, mainly involving muscles, tendons, joints and the nervous system.[10] The marketing authorizations of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin were restricted in the UK. They should not be used: 1) to treat self-limiting infections, or infections that are not severe; 2) to treat non-bacterial conditions or 3) to treat some mild to moderate infections (such as acute exacerbation of chronic

bronchitis and chronic obstructive pulmonary disease), unless other antibiotics that are commonly recommended for these infections are not appropriate.[10] Ciprofloxacin or levofloxacin should not be prescribed for uncomplicated cystitis unless other antibiotics that are commonly recommended are not appropriate.[10]

Fluoroquinolones should be avoided when treating infections in people who have previously experienced serious adverse events with FQs.[10] They should be used with caution especially in people who are at higher risk of tendon injury, such as people older than 60 years, or people with kidney problems or who have had an organ transplant.[10] Using a FQ together with a corticosteroid should be avoided because the risk of FQ-induced tendinitis and tendon rupture may be exacerbated.[10] The MHRA recommends that people should be advised to stop treatment with FQs at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects, and to contact their doctor immediately for further advice.[10]

After review, 2 guidelines were excluded due to poor quality.[48,49]

New Indications:
On 10/24/2019 delafloxacin (BAXDELA) received expanded FDA-approval to treat adults with CAP.[23] When delafloxacin was initially approved in 2018, it was only indicated for treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. Delafloxacin is indicated in adults for the treatment of CAP caused by the following susceptible microorganisms: *Streptococcus pneumoniae, Staphylococcus aureus (MSSA isolates only), Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydia pneumoniae, Legionella pneumophila, and Mycoplasma pneumoniae*.[23] Use in patients under 18 years of age is not recommended.[23]

For the expanded indication, delafloxacin was evaluated in a single noninferiority, multicenter, multinational, randomized, double-blind trial in adults with CAP (n = 859).[24] In this trial, delafloxacin every 12 hours was compared to moxifloxacin administered every 24 hours for 5 to 10 days. In the moxifloxacin arm, the investigator could switch patients to linezolid 600 mg every 12 hours if MRSA was confirmed (0.4% of participants).[24] Subjects with a history of QT prolongation or arrhythmias were excluded due to moxifloxacin being the comparator.[24] The primary end point was early clinical response (ECR), defined as improvement at 96 (±24) hours after the first dose of study drug.[24] In the ITT population analysis, ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group (difference -0.2%; 95% CI -4.4% to 4.1%).[24] Noninferiority of delafloxacin compared with moxifloxacin was demonstrated in patients with CAP. Treatment-emergent AEs that were considered at least possibly related to the study drug occurred in 65 subjects (15.2%) in the delafloxacin group and 54 (12.6%) in the moxifloxacin group.[24] In this trial, the most frequently reported AEs reported with delafloxacin administration were diarrhea and elevated liver function tests.[24]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ciprofloxacin Delafloxacin Gemifloxacin Levofloxacin Moxifloxacin Ofloxacin	CIPRO BAXDELA FACTIVE LEVAQUIN AVELOX OFLOXACIN	12/20/2018	FDA Safety Announcement[50]	The use of fluoroquinolone antibiotics has been associated with the rupture or dissection of aortic aneurysms. People at risk for aortic aneurysms include those with a history of peripheral atherosclerotic vascular diseases, hypertension, and certain genetic disorders that involve blood vessel changes such as Marfan syndrome and Ehlers-Danlos syndrome, and the elderly. Prescribe fluoroquinolones to these patients only when no other treatment options are available. FDA is requiring that a new warning about the rare but serious risk of aortic aneurysm be added to the prescribing information and patient Medication Guide of all fluoroquinolone antibiotics. In patients with a history of aneurysms, routine checkups and treatment for an aortic aneurysm can help prevent growth and rupture.[50]
Ciprofloxacin Delafloxacin Gemifloxacin Levofloxacin Moxifloxacin Ofloxacin	CIPRO BAXDELA FACTIVE LEVAQUIN AVELOX OFLOXACIN	7/10/2018	FDA Safety Announcement[51]	Fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. Health care professionals should be aware of the potential risk of hypoglycemia sometimes resulting in coma, occurring more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin. Alert patients of the symptoms of hypoglycemia and carefully monitor blood glucose levels in these patients, and discuss with them how to treat themselves if they have symptoms of hypoglycemia. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose. Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances and switch to a non-fluoroquinolone antibiotic if possible.[51]

Randomized Controlled Trials:

A total of 40 citations were manually reviewed from the initial literature search. After further review, 39 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Drekonja DM, et al[52] DB, PC, NI 2 VA Medical Centers	1. Ciprofloxacin 500 mg po BID x 7 days, followed by placebo for 7 days or 2. TMP-SMX 160/800 mg po BID x 7 days followed by placebo for 7 days Vs. 3. Ciprofloxacin 500 mg po BID x 14 days or 4. TMP-SMX 160/800mg po BID x 14 days	-Afebrile males aged 18 yrs and older -Prescribed ciprofloxacin or TMP-SMX for UTI -New onset: dysuria, urinary frequency, urinary urgency, perineal, flank or suprapubic pain N=272	Resolution of the initial UTI symptoms by day 14 after completion of active antibiotic treatment	Symptom Resolution 1. 7-day treatment: 122/131 (93.4%) 2. 14-day treatment: 111/123 (90.2%) Difference: 2.9% 1 sided 97.5% CI: -5.2 to infinity NI threshold met In afebrile males with suspected UTI, ciprofloxacin or TMP-SMX for 7 days was noninferior to 14 days with regard to resolution of UTI symptoms 14 days after initiation of antibiotic therapy.	-Urine cultures not completed to confirm bacterial UTI, which could bias results to finding no statistically significant difference between 7 vs. 14 days. -Study population limited to US veterans only. -Target enrollment of 290 subjects was not met, which may have impacted power to detect differences between groups -NI margin was based on expert opinion, rather than evidence

Abbreviations: BID = twice a day; DB = double blind; NI = noninferiority; PC = placebo control; po = oral; RCT = randomized clinical trial; TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection; VA = Veterans Affairs; yrs = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
ciprofloxacin	CIPRO	ORAL	SUS MC REC	Y
ciprofloxacin	CIPROFLOXACIN	ORAL	SUS MC REC	Y
ciprofloxacin HCl	CIPRO	ORAL	TABLET	Y
ciprofloxacin HCl	CIPROFLOXACIN HCL	ORAL	TABLET	Y
levofloxacin	LEVOFLOXACIN	ORAL	SOLUTION	Y
levofloxacin	LEVOFLOXACIN	ORAL	TABLET	Y
ciprofloxacin/ciprofloxa HCl	CIPRO XR	ORAL	TBMP 24HR	N
delafloxacin meglumine	BAXDELA	ORAL	TABLET	N
lomefloxacin HCl	MAXAQUIN	ORAL	TABLET	N
moxifloxacin HCl	MOXIFLOXACIN HCL	ORAL	TABLET	N
ofloxacin	OFLOXACIN	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection: A Randomized Clinical Trial. JAMA. 2021; 326(4):324-331. doi:10.1001/jama.2021.9899[52]

Objective To determine whether 7 days of treatment is noninferior to 14 days when using ciprofloxacin or trimethoprim/sulfamethoxazole to treat urinary tract infection (UTI) in afebrile men.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled noninferiority trial of afebrile men with presumed symptomatic UTI treated with ciprofloxacin or trimethoprim/sulfamethoxazole at 2 US Veterans Affairs medical centers (enrollment, April 2014 through December 2019; final follow-up, January 28, 2020). Of 1058 eligible men, 272 were randomized.

Interventions Participants continued the antibiotic prescribed by their treating clinician for 7 days of treatment and were randomized to receive continued antibiotic therapy (n = 136) or placebo (n = 136) for days 8 to 14 of treatment.

Main Outcomes and Measures the prespecified primary outcome was resolution of UTI symptoms by 14 days after completion of active antibiotic treatment. A noninferiority margin of 10% was selected. The as-treated population (participants who took ≥26 of 28 doses and missed no more than 2 consecutive doses) was used for the primary analysis, and a secondary analysis included all patients as randomized, regardless of treatment adherence. Secondary outcomes included recurrence of UTI symptoms and/or adverse events within 28 days of stopping study medication.

Results Among 272 patients (median [interquartile range] age, 69 [62-73] years) who were randomized, 100% completed the trial and 254 (93.4%) were included in the primary as-treated analysis. Symptom resolution occurred in 122/131 (93.1%) participants in the 7-day group vs 111/123 (90.2%) in the 14-day group (difference, 2.9% [1-sided 97.5% CI, –5.2% to ∞]), meeting the noninferiority criterion. In the secondary as-randomized analysis, symptom resolution occurred in 125/136 (91.9%) participants in the 7-day group vs 123/136 (90.4%) in the 14-day group (difference, 1.5% [1-sided 97.5% CI, –5.8% to ∞]) Recurrence of UTI symptoms occurred in 13/131 (9.9%) participants in the 7-day group vs 15/123 (12.9%) in the 14-day group (difference, –3.0% [95% CI, –10.8% to 6.2%]; *P* = .70). Adverse events occurred in 28/136 (20.6%) participants in the 7-day group vs 33/136 (24.3%) in the 14-day group.

Conclusions and Relevance Among afebrile men with suspected UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days of treatment with regard to resolution of UTI symptoms by 14 days after antibiotic therapy. The findings support the use of a 7-day course of ciprofloxacin or trimethoprim/sulfamethoxazole as an alternative to a 14-day course for treatment of afebrile men with UTI.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 4 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 7, 2021

1 exp Fluoroquinolones/	*27800*
2 exp Ciprofloxacin/	*10633*
3 exp Levofloxacin/	*3566*
4 exp Ofloxacin/	*5951*
5 exp Moxifloxacin.mp.	*2710*
6 exp Gemifloxacin.mp.	*279*
7 delafloxacin.mp.	*1326*
8 lomefloxacin.mp	*574*
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	*27945*
10 limit 9 to (English language and humans and yr="2018-Current" and clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	*398*
11 Administration, Oral/ or oral.mp.	*126144*
12 10 or 11	*40*