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, December 2nd, 2021 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)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. Quarterly Utilization Reports
B. Inhaled Cystic Fibrosis Drugs Literature Scan
C. Oncology Prior Authorization Updates
D. Orphan Drug Policy Updates
   1. Public Comment

III. DUR ACTIVITIES

1:25 PM	A. ProDUR Report	L. Starkweather (Gainwell)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)

1. COVID-19 Vaccine Update
2. Deprescribing Techniques to Minimize Safety Issues Associated with Inappropriate Polypharmacy

IV. DUR OLD BUSINESS

1:40 PM	A. Evkeeza™ (evinacumab-dgnb) Prior Authorization Update	M. Herink (OSU)

1. Prior Authorization Update
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

1:50 PM	B. Spravato® (esketamine) Safety Edit Update 1. Safety Edit Update 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
	V. DUR NEW BUSINESS	
2:05 PM	A. HIV Pre-Exposure Prophylaxis Drug Use Evaluation 1. Drug Use Evaluation 2. Public Comment 3. Discussion and Clinical Recommendations to OHA	S. Servid (OSU)
	VI. PREFERRED DRUG LIST NEW BUSINESS	
2:25 PM	A. Glucagon Class Update with New Drug Evaluation 1. Class Update 2. Zegalogue® (dasiglucagon) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	K. Sentena (OSU)
2:40 PM	B. Paroxysmal Nocturnal Hemoglobinuria Focused Class Update with New Drug Evaluation 1. Focused Class Update/ Prior Authorization Criteria 2. Empaveli™ (pegcetacoplan) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
2:55 PM	BREAK	
3:10 PM	C. GnRH Modifiers Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Myfembree® (relugolix; estradiol; norethindrone) New Drug Evaluation 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:30 PM	D. Growth Hormone Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Skytrofa™ (lonapegsomatropin-tcgd) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:50 pm	E. Bile Therapy Literature Scan/Prior Authorization Update 1. Literature Scan/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)

4:05 PM	VII. EXECUTIVE SESSION
4:40 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS
	IX. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021
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, Oregon Health Forum	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, October 7th, 2021 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: Cathy Zehrung, RPh; Cat Livingston, MD; Stacy Ramirez, PharmD; Tim Langford, PharmD; Caryn Mickelson, PharmD; Robin Moody, MPH; William Origer, MD

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

Audience: Amy Burns, AllCare CCO; Bill McDougall, Biogen; Brandie Feger, Advanced Health; Camille Kerr, Regeneron; Carly Gostanian, PacificSource; Carmen Oliver, BioHaven; **Carrie Johnson, Amgen***; Dave West, United Therapeutics; **David Bedich, ParaPro; Jennifer Shear, Teva***; **Ann Thomas, OHA Center for Public Health Practice***; Laurie Krekemeyer; Lindsey Walter, Novartis; Lisa Dunn; Lori Howarth, Bayer; **Christine Hui, United Therapeutics***; Lynda Finch, Biogen; **Margaret Olmon, AbbVie***; Mark Kantor, AllCare Health; Matt Worthy, OHSU; Melissa Snider, Gilead Science; Michael Foster, BMS; Mike Willett, Pfizer; **Andrew Seaman, OHSU***; Olaf Reinwald, GBT; **Lorren Sandt, Caring Ambassadors***; Peter Barrio, United Therapeutics; Rachel Hartman, IHN CCO; Rick Frees, Vertex; Robert Pearce, Teva; Saghi Maleki, Takeda; Sophia Yun, Janssen; Tiffany Jones, PacificSource; Tina Andrews, Umpqua Health Aliance; Tina Hartman, Jazz Pharmaceuticals; Trent Taylor, JNJ; Venus Holder, Lilly USA; **Yuval Zabar, Biogen*; John Clark, UMASS***

(*) Provided verbal testimony

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Written testimony: Posted to OSU Website

I. CALL TO ORDER

A. Roll Call & Introductions
   - Called to order at approx. 1:05 p.m., introductions by staff and committee
B. Approval of Agenda
C. Conflict of Interest Declaration – no new conflicts of interest were declared
D. Approval of August 2021 Minutes presented by Roger Citron
   ACTION: Motion to approve, 2nd, all in favor
E. Department Update – Trevor Douglass

II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization (PA) Updates
   Recommendations:
   - Add the following new FDA-approved antineoplastic agents to Table 1 in the Oncology Agents prior authorization (PA) criteria: Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn); and Welireg™ (belzutifan)
B. Orphan Drug Policy Updates
   Recommendations:
   - Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of Ryplazim® (plasminogen, human-tvmh) and Rezurock™ (belumosudil mesylate) based on FDA-approved labeling
C. Inhaled Anticholinergic Literature Scan
D. Antiepileptics (non-injectable) Literature Scan
   Recommendations:
   - No PDL changes recommended based on the clinical evidence
   - Evaluate costs in executive session
   ACTION: Motion to approve, 2nd, all in favor

III. PREFERRED DRUG LIST NEW BUSINESS

A. Biologics for Autoimmune Disorders Class Update: Deanna Moretz, PharmD
   Recommendations:
   - Make no changes to the PDL based on the review of recent clinical evidence
   - Rename the class "Targeted Immune Modulators" and modify the PA criteria to include expanded ages and indications

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- Modify the "Multiple Sclerosis Oral Agents" PA criteria to include the expanded indication for ozanimod in adults with moderate-to severe ulcerative colitis
- Evaluate costs in executive session

Public Comment: Maggi Olmon, AbbVie; Carrie Johnson, Amgen
ACTION: Motion to approve, 2nd, all in favor

B. Calcitonin Gene-Related Peptide (CGRP) Inhibitors Class Update: Kathy Sentena, PharmD

Recommendations:
- Make no changes to the PDL based on the review of recent clinical evidence
- Update the PA criteria to clarify the difference between acute (abortive) and prophylactic (preventative) treatment
- Update the recommended drugs for cluster headache, and to
- Evaluate costs in executive session

Public Comment: Jennifer Shear, Teva; Maggi Olmon, AbbVie; Carrie Johnson, Amgen
ACTION: The Committee recommended implementing the proposed recommendations after adding a question to require providers assess for uncontrolled hypertension prior to initiation of therapy for applicable agents - including Aimovig®
Motion to approve, 2nd, All in favor

C. Hepatitis C Direct Acting Antivirals (DAA): Megan Herink, PharmD

Recommendations:
- Update the PA criteria and treatment table to include new pediatric indications and clerical updates
- Evaluate costs in executive session

Public Comment: Maggi Olmon, AbbVie; Ann Thomas, OHA Public Health; Andy Seaman, Old Town Clinic/Central City Concern; Lorren Sandt, Caring Ambassadors
ACTION: The Committee requested staff evaluate financial impacts, search for any new clinical information or data from other state programs who have opened access to consider removal of PA criteria for preferred agents and treatment of acute therapy
Motion to approve, 2nd, All in favor

D. Pulmonary Arterial Hypertension (PAH) Class Update: Sarah Servid, PharmD

Recommendations:
- Make no changes to the PDL based on the review of recent clinical evidence
- Update the PA criteria to include expanded indications
- Evaluate costs in executive session

Public Comment: Christine Hui, United Therapeutics
ACTION: Motion to approve, 2nd, all in favor

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E. Alzheimer's Disease Drug Class Update and New Drug Evaluation: David Engen, PharmD
Recommendations:
- Maintain aducanumab as non-preferred on the PDL
- Implement proposed PA criteria to ensure appropriate use
- Evaluate costs in Executive Session
Public Comment: Yuval Zabar, Biogen
ACTION: The Committee recommended amending question #7 to mirror mild disease, as defined in studies including a Mini-Mental Status Exam (MMSE) between 24-30 and Clinical Dementia Rating-Global Score (CDR-GS) of 0.5, and to modify renewal criteria to prevent continuation of therapy in patients with any evidence of microhemorrhage. The Committee also recommended the OHA consider not covering Aduhelm™ due to its significant toxicity and unproven clinical benefit
Motion to approve, 2nd, All in favor

F. Topical Antiparasitic Agents: Sara Fletcher, PharmD
Recommendations:
- Maintain abametapir as non-preferred on the PDL
- Include ivermectin cream (Soolantra®) in the topical antiparasitic class and designate as non-preferred
- No other changes to the PDL based on recent evidence
- Evaluate costs in executive session
Public Comment: John Clark, UMASS; David Bedich, ParaPro
Motion to Approve, 2nd, all in favor

IV. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; William Origer, MD; Cathy Zehrung, RPh; Cat Livingston, MD; Tim Langford, PharmD; Caryn Mickelson, PharmD; Robin Moody, MPH;

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

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V. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Inhaled Anticholinergic Literature Scan**
Recommendation: Make Combivent® Respimat® & Incruse® Ellipta® preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. **Antiepileptics (non-injectable) Literature Scan**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

C. **Targeted Immune Modulators**
Recommendation: Make Cosentyx® preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

D. **CGRP Inhibitors**
Recommendation: Make Aimovig® preferred and Emgality® non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

E. **Hepatitis C DAAs**
Recommendation: Make branded Epclusa® non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

F. **PAH Drug Class**
Recommendation: No changes to the PDL are recommended
ACTION: Motion to approve, 2nd, all in favor

G. **Alzheimer's Disease Drug Class**
Recommendation: Make donepezil, rivastigmine, memantine, and Namzaric® preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

H. **Topical Antiparasitic Agents**
Recommendation: Make Soolantral® and Vanalice™ non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2020 - March 2021

Eligibility	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Total Members (FFS & Encounter)	1,026,262	1,039,871	1,052,702	1,065,127	1,078,611	1,091,643	1,105,304	1,124,250	1,142,287	1,155,608	1,165,327	1,176,534	1,101,961
FFS Members	109,012	94,359	89,482	92,036	97,318	96,060	99,759	110,699	110,136	110,971	104,212	106,887	101,744
OHP Basic with Medicare	7,613	7,275	7,121	7,235	7,333	7,140	7,395	8,031	7,925	7,781	7,599	7,743	7,516
OHP Basic without Medicare	11,470	11,412	11,281	11,469	11,624	11,493	11,546	11,692	11,422	11,524	11,224	11,074	11,436
ACA	89,929	75,672	71,080	73,332	78,361	77,427	80,818	90,976	90,789	91,666	85,389	88,070	82,792
Encounter Members	917,250	945,512	963,220	973,091	981,293	995,583	1,005,545	1,013,551	1,032,151	1,044,637	1,061,115	1,069,647	1,000,216
OHP Basic with Medicare	71,584	72,135	72,516	72,537	72,713	73,520	74,103	74,533	75,527	76,328	77,441	78,598	74,295
OHP Basic without Medicare	63,059	62,873	62,810	62,587	64,059	65,009	65,428	65,582	66,083	67,172	67,155	66,975	64,899
ACA	782,607	810,504	827,894	837,967	844,521	857,054	866,014	873,436	890,541	901,137	916,519	924,074	861,022

Gross Cost Figures for Drugs	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	YTD Sum
Total Amount Paid (FFS & Encounter)	$85,288,789	$81,924,100	$88,909,908	$90,490,422	$88,020,808	$88,732,406	$89,902,214	$86,308,264	$97,755,734	$92,977,048	$89,172,154	$104,697,710	$1,084,179,557
Mental Health Carve-Out Drugs	$9,049,995	$8,781,442	$9,436,145	$9,468,980	$9,174,782	$9,229,001	$9,451,196	$9,149,457	$10,069,992	$10,194,514	$10,203,228	$12,119,749	$116,328,481
OHP Basic with Medicare	$29,898	$29,851	$35,823	$32,866	$30,054	$38,156	$25,916	$26,636	$43,711	$26,605	$27,401	$8,529	$355,444
OHP Basic without Medicare	$3,476,896	$3,282,336	$3,641,928	$3,564,559	$3,591,312	$3,566,715	$3,691,687	$3,621,907	$3,904,148	$4,012,212	$4,078,117	$4,686,766	$45,118,585
ACA	$5,495,257	$5,418,162	$5,712,276	$5,829,824	$5,503,762	$5,577,427	$5,686,367	$5,446,049	$6,068,088	$6,101,923	$6,039,256	$7,355,710	$70,234,102
FFS Physical Health Drugs	$2,914,340	$2,526,465	$2,568,409	$2,559,091	$2,371,978	$2,482,914	$2,574,584	$2,299,662	$2,595,524	$4,481,798	$4,151,565	$5,037,115	$36,563,445
OHP Basic with Medicare	$52,596	$44,159	$51,909	$56,118	$48,367	$48,223	$47,671	$43,752	$48,631	$160,401	$142,100	$157,260	$901,186
OHP Basic without Medicare	$1,003,610	$909,086	$912,517	$870,473	$848,072	$867,036	$922,623	$775,671	$942,688	$1,360,983	$1,131,608	$1,271,572	$11,815,940
ACA	$1,738,757	$1,450,562	$1,461,367	$1,484,344	$1,348,971	$1,437,998	$1,491,424	$1,366,591	$1,474,179	$2,841,781	$2,761,612	$3,488,974	$22,346,560
FFS Physician Administered Drugs	$1,142,955	$1,160,834	$1,568,668	$1,575,014	$1,142,451	$1,096,964	$1,629,448	$1,214,886	$1,173,590	$1,314,056	$1,618,068	$1,232,941	$15,869,876
OHP Basic with Medicare	$103,024	$90,218	$116,424	$130,997	$88,598	$100,595	$86,755	$107,077	$99,531	$167,071	$143,936	$149,634	$1,383,859
OHP Basic without Medicare	$141,949	$365,022	$594,681	$495,740	$239,681	$241,384	$607,085	$345,949	$211,858	$169,013	$638,278	$155,579	$4,206,218
ACA	$485,948	$335,911	$366,902	$391,611	$374,581	$390,711	$461,820	$352,285	$466,357	$489,931	$456,968	$437,304	$5,010,329
Encounter Physical Health Drugs	$57,711,340	$54,869,171	$58,786,420	$60,906,332	$59,350,860	$60,162,054	$59,979,727	$58,139,796	$63,075,811	$60,786,603	$58,138,061	$68,409,153	$720,315,327
OHP Basic with Medicare	$666,871	$668,580	$729,962	$677,708	$652,717	$742,679	$758,719	$718,200	$761,348	$621,554	$587,912	$381,369	$7,967,619
OHP Basic without Medicare	$14,083,368	$13,191,709	$14,066,119	$14,034,931	$14,323,451	$14,660,407	$14,227,568	$14,407,810	$15,841,867	$14,932,450	$14,191,204	$16,785,861	$174,746,747
ACA	$42,371,606	$40,376,972	$43,412,570	$45,564,822	$43,749,115	$44,126,201	$44,256,283	$42,329,144	$45,801,824	$44,570,112	$42,670,168	$50,360,851	$529,589,669
Encounter Physician Administered Drugs	$14,470,160	$14,586,188	$16,550,266	$15,981,004	$15,980,736	$15,761,473	$16,267,260	$15,504,463	$20,840,817	$16,200,076	$15,061,233	$17,898,752	$195,102,428
OHP Basic with Medicare	$496,230	$595,728	$635,732	$642,028	$606,226	$691,385	$682,925	$629,013	$621,831	$697,831	$621,342	$924,578	$7,844,848
OHP Basic without Medicare	$3,604,072	$3,419,120	$3,585,227	$3,290,420	$3,422,741	$3,624,685	$3,714,356	$3,472,377	$7,186,572	$3,719,302	$3,038,219	$3,730,940	$45,808,031
ACA	$10,166,955	$10,252,458	$11,949,695	$11,674,562	$11,553,409	$10,978,601	$11,433,156	$10,874,574	$12,698,773	$11,343,814	$10,945,325	$12,895,197	$136,766,519

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: October 21, 2021

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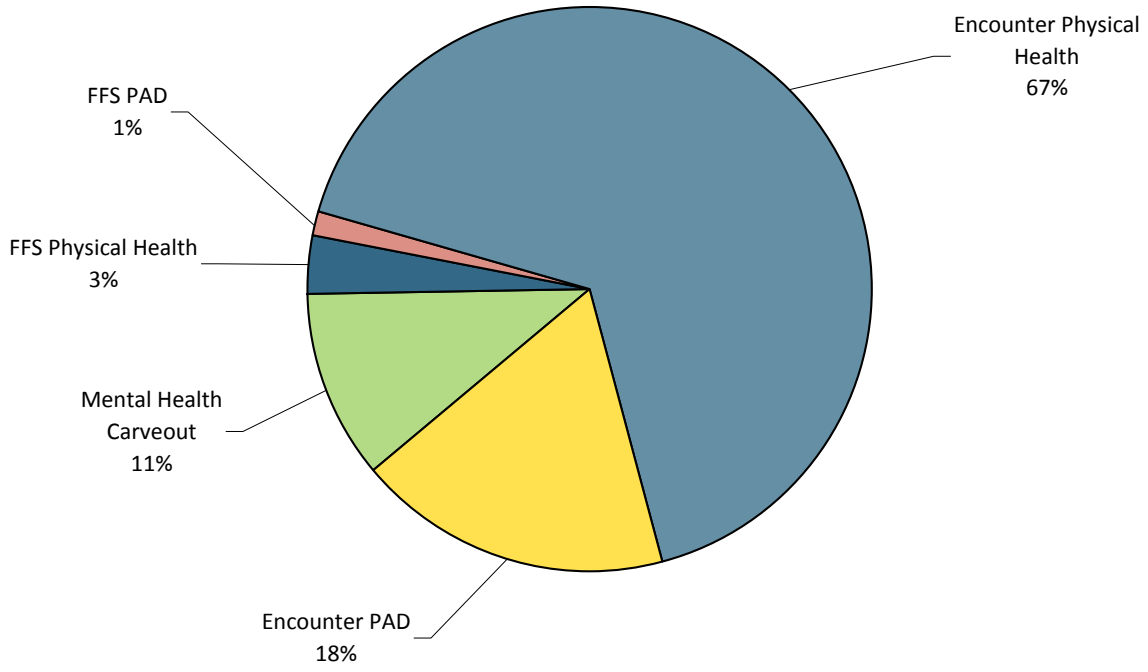
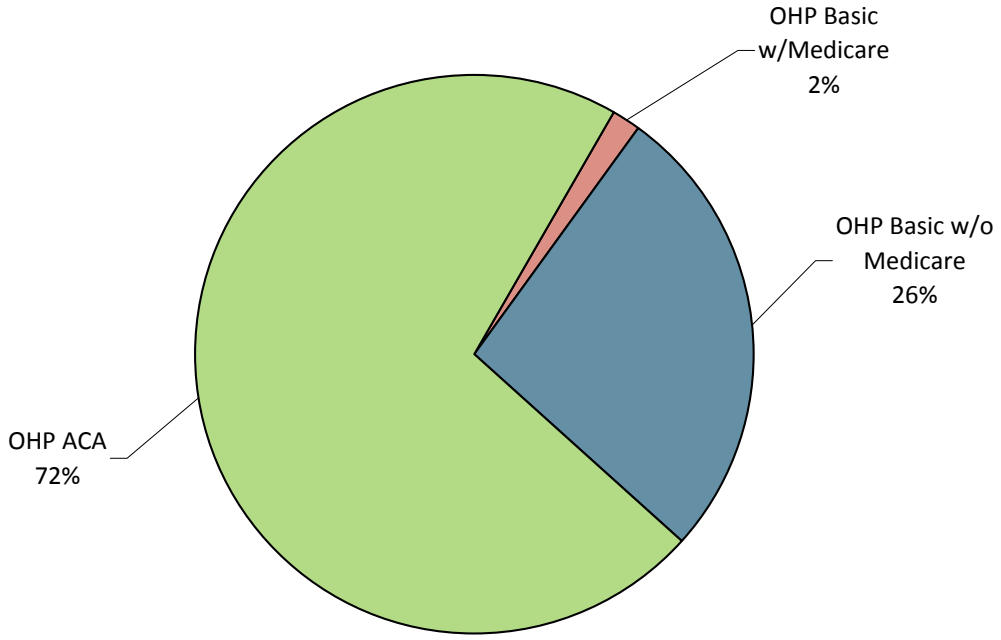
YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: October 21, 2021

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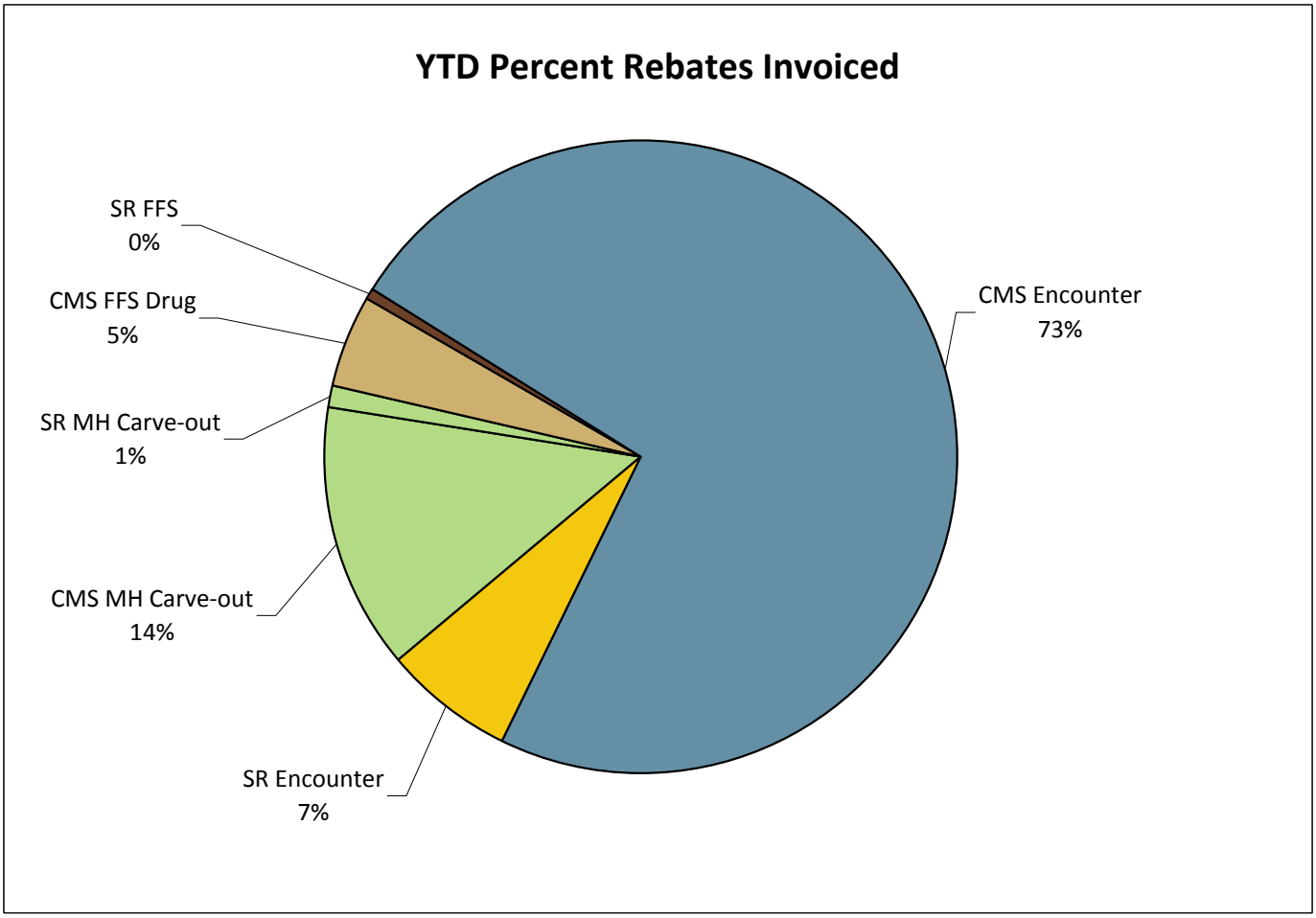
Pharmacy Utilization Summary Report: April 2020 - March 2021

Quarterly Rebates Invoiced	2020-Q2	2020-Q3	2020-Q4	2021-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$108,010,853	$115,851,694	$109,001,436	$117,515,606	$450,379,589
CMS MH Carve-out	$12,821,867	$18,672,661	$13,089,007	$16,648,773	$61,232,308
SR MH Carve-out	$1,330,612	$1,335,658	$1,460,762	$1,485,656	$5,612,687
CMS FFS Drug	$5,398,225	$4,685,150	$4,664,616	$6,040,817	$20,788,808
SR FFS	$473,832	$458,213	$512,651	$540,643	$1,985,339
CMS Encounter	$80,940,047	$83,368,524	$81,711,301	$84,545,501	$330,565,373
SR Encounter	$7,046,270	$7,331,488	$7,563,099	$8,254,216	$30,195,073

Quaterly Net Drug Costs	2020-Q2	2020-Q3	2020-Q4	2021-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$148,111,945	$151,391,941	$164,964,777	$169,331,306	$633,799,969
Mental Health Carve-Out Drugs	$13,115,103	$7,864,444	$14,120,876	$14,383,063	$49,483,486
FFS Phys Health + PAD	$6,009,614	$6,085,050	$6,310,427	$11,254,082	$29,659,173
Encounter Phys Health + PAD	$128,987,228	$137,442,447	$144,533,474	$143,694,161	$554,657,310



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

Last Updated: October 21, 2021

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: April 2020 - March 2021

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$83.11	$78.78	$84.46	$84.96	$81.61	$81.28	$81.34	$76.77	$85.58	$80.46	$76.52	$88.99	$81.99
Mental Health Carve-Out Drugs	$8.82	$8.44	$8.96	$8.89	$8.51	$8.45	$8.55	$8.14	$8.82	$8.82	$8.76	$10.30	$8.79
FFS Physical Health Drugs	$26.73	$26.78	$28.70	$27.81	$24.37	$25.85	$25.81	$20.77	$23.57	$40.39	$39.84	$47.13	$29.81
FFS Physician Administered Drugs	$10.48	$12.30	$17.53	$17.11	$11.74	$11.42	$16.33	$10.97	$10.66	$11.84	$15.53	$11.53	$13.12
Encounter Physical Health Drugs	$62.92	$58.03	$61.03	$62.59	$60.48	$60.43	$59.65	$57.36	$61.11	$58.19	$54.79	$63.95	$60.04
Encounter Physician Administered Drugs	$15.78	$15.43	$17.18	$16.42	$16.29	$15.83	$16.18	$15.30	$20.19	$15.51	$14.19	$16.73	$16.25

Claim Counts	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Total Claim Count (FFS & Encounter)	983,456	991,176	1,049,420	1,058,135	1,039,312	1,056,097	1,088,816	1,032,761	1,090,694	1,069,610	1,008,851	1,160,379	1,052,392
Mental Health Carve-Out Drugs	164,849	164,261	172,259	174,471	171,634	173,404	177,456	174,302	186,788	182,989	172,737	197,156	176,026
FFS Physical Health Drugs	41,248	37,711	39,218	36,784	35,560	36,442	37,803	33,998	36,603	37,978	35,845	42,009	37,600
FFS Physician Administered Drugs	8,918	9,768	10,016	9,989	10,114	10,099	10,463	9,885	10,220	11,074	9,926	11,080	10,129
Encounter Physical Health Drugs	685,355	677,527	715,150	723,368	706,084	722,795	743,134	704,754	743,875	722,925	682,011	788,267	717,937
Encounter Physician Administered Drugs	83,086	101,909	112,777	113,523	115,920	113,357	119,960	109,822	113,208	114,644	108,332	121,867	110,700

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$86.72	$82.65	$84.72	$85.52	$84.69	$84.02	$82.57	$83.57	$89.63	$86.93	$88.39	$90.23	$85.80
Mental Health Carve-Out Drugs	$54.90	$53.46	$54.78	$54.27	$53.46	$53.22	$53.26	$52.49	$53.91	$55.71	$59.07	$61.47	$55.00
FFS Physical Health Drugs	$70.65	$67.00	$65.49	$69.57	$66.70	$68.13	$68.11	$67.64	$70.91	$118.01	$115.82	$119.91	$80.66
FFS Physician Administered Drugs	$128.16	$118.84	$156.62	$157.67	$112.96	$108.62	$155.73	$122.90	$114.83	$118.66	$163.01	$111.28	$130.77
Encounter Physical Health Drugs	$84.21	$80.98	$82.20	$84.20	$84.06	$83.24	$80.71	$82.50	$84.79	$84.08	$85.25	$86.78	$83.58
Encounter Physician Administered Drugs	$174.16	$143.13	$146.75	$140.77	$137.86	$139.04	$135.61	$141.18	$184.09	$141.31	$139.03	$146.87	$147.48

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.53	$19.17	$19.47	$20.31	$20.24	$20.58	$20.10	$20.76	$21.35	$23.42	$23.47	$23.02	$20.95
Mental Health Carve-Out Drugs	$16.77	$16.87	$16.94	$16.83	$16.79	$16.33	$16.35	$16.38	$16.55	$17.98	$17.97	$17.58	$16.95
FFS Physical Health Drugs	$20.98	$20.19	$19.93	$20.27	$20.57	$21.21	$21.14	$21.28	$22.63	$70.05	$70.61	$74.02	$33.57
Encounter Physical Health Drugs	$20.19	$19.73	$20.11	$21.24	$21.15	$21.69	$21.06	$21.95	$22.62	$22.65	$22.72	$22.05	$21.43

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$548.61	$523.17	$543.39	$556.48	$550.50	$510.36	$476.95	$507.86	$548.75	$552.22	$556.81	$550.05	$535.43
Mental Health Carve-Out Drugs	$1,114.54	$1,103.39	$1,115.05	$1,108.05	$1,104.82	$1,101.09	$1,104.96	$1,083.85	$1,098.68	$1,125.99	$1,109.53	$1,053.65	$1,101.97
FFS Physical Health Drugs	$282.08	$265.54	$261.01	$280.23	$274.94	$271.38	$261.68	$264.29	$281.92	$334.24	$305.55	$292.29	$281.26
Encounter Physical Health Drugs	$535.13	$507.24	$528.50	$540.80	$533.99	$490.84	$455.49	$488.02	$529.80	$528.60	$534.47	$530.81	$516.98

Generic Drug Use Percentage	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Generic Drug Use Percentage	88.9%	88.9%	89.1%	89.2%	89.2%	88.5%	88.0%	88.6%	89.2%	89.3%	89.1%	88.6%	88.9%
Mental Health Carve-Out Drugs	96.5%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.5%	96.6%	96.2%	95.8%	96.5%
FFS Physical Health Drugs	81.0%	80.9%	81.1%	81.0%	81.9%	81.2%	80.5%	80.9%	81.4%	81.8%	80.8%	79.0%	81.0%
Encounter Physical Health Drugs	87.6%	87.4%	87.8%	87.9%	87.7%	86.9%	86.3%	87.0%	87.7%	87.9%	87.8%	87.3%	87.4%

Preferred Drug Use Percentage	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Avg Monthly
Preferred Drug Use Percentage	84.87%	84.75%	85.03%	85.37%	85.29%	86.77%	86.68%	86.67%	86.65%	86.70%	86.60%	86.55%	86.0%
Mental Health Carve-Out Drugs	73.16%	72.87%	73.05%	72.83%	72.85%	77.40%	77.28%	77.16%	77.37%	77.24%	76.90%	76.91%	75.4%
FFS Physical Health Drugs	89.22%	89.18%	88.96%	94.22%	94.23%	94.69%	94.36%	94.28%	94.78%	94.42%	94.16%	94.19%	93.1%
Encounter Physical Health Drugs	87.38%	87.34%	87.64%	87.92%	87.85%	88.63%	88.57%	88.67%	88.58%	88.69%	88.66%	88.59%	88.2%

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

Last Updated: October 21, 2021

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2021

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,937,198	15.9%	5,718	$1,213	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,316,597	7.6%	1,543	$2,149	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,613,263	6.0%	2,306	$1,133	Y
4	STRATTERA*	ADHD Drugs	$2,479,069	5.7%	5,405	$459	Y
5	INVEGA	Antipsychotics, 2nd Gen	$2,296,678	5.3%	1,772	$1,296	V
6	REXULTI	Antipsychotics, 2nd Gen	$1,923,975	4.4%	1,706	$1,128	V
7	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,848,692	4.2%	888	$2,082	Y
8	INVEGA TRINZA	Antipsychotics, Parenteral	$882,326	2.0%	137	$6,440	Y
9	ARISTADA	Antipsychotics, Parenteral	$759,415	1.7%	326	$2,329	Y
10	TRINTELLIX	Antidepressants	$729,953	1.7%	1,763	$414	V
11	SERTRALINE HCL	Antidepressants	$577,848	1.3%	56,851	$10	Y
12	BUPROPION XL	Antidepressants	$523,180	1.2%	37,040	$14	Y
13	DULOXETINE HCL	Antidepressants	$519,860	1.2%	35,560	$15	Y
14	VIIBRYD	Antidepressants	$517,503	1.2%	1,699	$305	V
15	FLUOXETINE HCL	Antidepressants	$469,876	1.1%	40,999	$11	Y
16	TRAZODONE HCL	Antidepressants	$448,050	1.0%	44,971	$10	
17	ESCITALOPRAM OXALATE	Antidepressants	$367,681	0.8%	37,136	$10	Y
18	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$312,535	0.7%	24,901	$13	
19	LAMOTRIGINE	Antiepileptics (non-injectable)	$299,557	0.7%	27,776	$11	Y
20	BIKTARVY	HIV	$284,065	0.7%	100	$2,841	Y
21	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$276,456	0.6%	308	$898	Y
22	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$258,638	0.6%	24	$10,777	Y
23	CHOLBAM*	Bile Therapy	$248,984	0.6%	6	$41,497	N
24	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$237,552	0.5%	2,817	$84	V
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$233,740	0.5%	18,563	$13	Y
26	VENLAFAXINE HCL ER	Antidepressants	$224,232	0.5%	18,443	$12	Y
27	PFIZER COVID-19 VACCINE (EUA)	STC 90 - Biologicals	$218,097	0.5%	5,472	$40	
28	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$212,828	0.5%	19,075	$11	Y
29	Inj Pembrolizumab	Physican Administered Drug	$208,149	0.5%	43	$4,841	
30	BUPROPION XL	Antidepressants	$197,662	0.5%	985	$201	V
31	AMITRIPTYLINE HCL*	Antidepressants	$193,443	0.4%	14,322	$14	Y
32	VENLAFAXINE HCL ER	Antidepressants	$191,837	0.4%	2,232	$86	V
33	CITALOPRAM HBR	Antidepressants	$190,566	0.4%	21,829	$9	Y
34	SPRAVATO*	Antidepressants	$175,522	0.4%	139	$1,263	V
35	LAMICTAL ODT	Antiepileptics (non-injectable)	$164,325	0.4%	199	$826	V
36	Elosulfase Alfa, Injection	Physican Administered Drug	$163,829	0.4%	12	$13,652	
37	LANTUS SOLOSTAR*	Diabetes, Insulins	$163,247	0.4%	489	$334	Y
38	MIRTAZAPINE	Antidepressants	$156,348	0.4%	10,757	$15	Y
39	TRIKAFTA*	Cystic Fibrosis	$156,193	0.4%	16	$9,762	N
40	WELLBUTRIN XL	Antidepressants	$154,225	0.4%	186	$829	Y
		Top 40 Aggregate:	**$32,133,194**		**444,514**	**$2,676**	
		All FFS Drugs Totals:	**$43,605,526**		**685,755**	**$569**	

*** Drug requires Prior Authorization**

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

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2021

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	BIKTARVY	HIV	$284,065	3.0%	100	$2,841	Y
2	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$258,638	2.7%	24	$10,777	Y
3	CHOLBAM*	Bile Therapy	$248,984	2.6%	6	$41,497	N
4	PFIZER COVID-19 VACCINE (EUA)	STC 90 - Biologicals	$218,097	2.3%	5,472	$40	
5	Inj Pembrolizumab	Physican Administered Drug	$208,149	2.2%	43	$4,841	
6	Elosulfase Alfa, Injection	Physican Administered Drug	$163,829	1.7%	12	$13,652	
7	LANTUS SOLOSTAR*	Diabetes, Insulins	$163,247	1.7%	489	$334	Y
8	TRIKAFTA*	Cystic Fibrosis	$156,193	1.6%	16	$9,762	N
9	CONCERTA*	ADHD Drugs	$144,748	1.5%	439	$330	N
10	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$142,697	1.5%	585	$244	
11	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$127,140	1.3%	7	$18,163	
12	DEMSER	STC 71 - Other Hypotensives	$117,196	1.2%	2	$58,598	
13	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$116,293	1.2%	222	$524	Y
14	ELIQUIS	Anticoagulants, Oral and SQ	$111,016	1.2%	291	$381	Y
15	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$104,847	1.1%	2,475	$42	Y
16	IBRANCE*	Antineoplastics, Newer	$104,662	1.1%	8	$13,083	
17	VYVANSE*	ADHD Drugs	$103,822	1.1%	633	$164	Y
18	VIMPAT	Antiepileptics (non-injectable)	$99,320	1.0%	219	$454	Y
19	STELARA*	Targeted Immune Modulators	$99,103	1.0%	13	$7,623	N
20	DARAPRIM	STC 32 - Antimalarials	$92,996	1.0%	2	$46,498	
21	Etonogestrel Implant System	Physican Administered Drug	$92,728	1.0%	137	$677	
22	HUMIRA(CF) PEN*	Targeted Immune Modulators	$90,791	0.9%	27	$3,363	Y
23	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$89,566	0.9%	5	$17,913	Y
24	Inj. Pemetrexed Nos 10mg	Physican Administered Drug	$85,984	0.9%	40	$2,150	
25	Aflibercept Injection	Physican Administered Drug	$84,540	0.9%	173	$489	
26	ENBREL SURECLICK*	Targeted Immune Modulators	$84,291	0.9%	19	$4,436	Y
27	SABRIL	Antiepileptics (non-injectable)	$84,115	0.9%	2	$42,057	N
28	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$78,350	0.8%	1,191	$66	Y
29	Pegaspargase Injection	Physican Administered Drug	$66,497	0.7%	2	$33,249	
30	FLOVENT HFA	Corticosteroids, Inhaled	$64,798	0.7%	437	$148	Y
31	MODERNA COVID-19 VACCINE (EUA	STC 90 - Biologicals	$64,771	0.7%	1,647	$39	
32	PROMACTA	Thrombocytopenia Drugs	$64,340	0.7%	7	$9,191	Y
33	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$63,489	0.7%	6	$10,582	N
34	AFINITOR DISPERZ*	Antineoplastics, Newer	$63,475	0.7%	9	$7,053	
35	Mirena, 52 Mg	Physican Administered Drug	$63,323	0.7%	107	$592	
36	NORDITROPIN FLEXPRO*	Growth Hormones	$61,028	0.6%	27	$2,260	Y
37	REVLIMID	STC 30 - Antineoplastic	$56,053	0.6%	5	$11,211	
38	Pertuzu, Trastuzu, 10 Mg	Physican Administered Drug	$55,510	0.6%	4	$13,877	
39	Infliximab Not Biosimil 10mg	Physican Administered Drug	$55,399	0.6%	55	$1,007	
40	ETONOGESTREL-ETHINYL ESTRADIOI	STC 63 - Oral Contraceptives	$53,931	0.6%	283	$191	
		Top 40 Aggregate:	**$4,488,017**		**15,241**	**$9,760**	
		All FFS Drugs Totals:	**$9,580,072**		**118,452**	**$583**	

*** Drug requires Prior Authorization**

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

Last updated: October 21, 2021

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Drug Class Literature Scan: Inhaled Drugs for Cystic Fibrosis

Date of Review: December 2021

Date of Last Review: January 2016
Literature Search: 10/01/15 – 09/03/21

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

Conclusions:

- The following literature was identified from this scan: 6 systematic reviews and meta-analyses, 2 clinical practice guidelines, 1 new drug, 1 randomized controlled trial and 2 new safety alerts.
- A Cochrane review found inhaled mannitol 400 mg was more effective than control (subtherapeutic mannitol 50 mg) for improvement in lung function based on forced expiratory volume in one second (FEV_1) and percent FEV_1 -predicted (FEV_1%), in studies lasting up to 6 months in patients with cystic fibrosis (CF).[1]
- Dornase alfa was studied in a Cochrane review and was found to be more effective than placebo for improving lung function and reducing pulmonary exacerbations.[2] Studies that compared dornase alfa to hypertonic saline or inhaled mannitol (up to 475 mg) were not conclusive of a clear benefit of one intervention over another based on low quality evidence.[2]
- A Cochrane review evaluated antibiotic strategies for eradicating *Pseudomonas aeruginosa* (*P. aeruginosa*) in adults and children with CF. Inhaled tobramycin was more effective than placebo for microbiological eradication of *P. aeruginosa* from the respiratory tract.[3] All other findings for inhaled antibiotics demonstrated no difference between comparisons and most of the evidence was of low to very low quality.
- A Cochrane review studied therapies for preventing recurrence of infection with *P. aeruginosa* in individuals with CF.[4] Only one study met inclusion criteria. The trial compared inhaled tobramycin 300 mg twice daily every 3 months without regard to culture results (cycled therapy) versus inhaled tobramycin 300 mg twice daily only in the 3-month period after positive culture results for *P. aeruginosa* (culture-based therapy). Culture-based therapy was more likely to have recurrence of infection by the final study visit (up to 563 days) compared to those in the cycled therapy (hazard ratio [HR] 2.04; 95% confidence interval [CI], 1.28 to 3.26).[4]
- One Cochrane review evaluated inhaled antibiotics for the treatment of pulmonary exacerbations and a second Cochrane review studied nebulized hypertonic saline in patients with CF. Both reviews were not able to draw strong conclusions due to low or very low quality of evidence available for analysis.[5,6]
- National Institute for Health and Care Excellence (NICE) Guidelines recommend the use of dornase alfa first-line for patients with CF requiring mucoactive therapy.[7] The treatment of *P. aeruginosa* should include inhaled antibiotics (e.g., tobramycin or aztreonam) in combination with oral or intravenous (IV) antibiotics. Tobramycin dry-powder inhaler (DPI) can be considered for patients who are deemed to be appropriate candidates for nebulized tobramycin.[7] These recommendations are also supported by NICE quality standards for patients with CF.[8]

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- The Food and Drug Administration (FDA) approved mannitol DPI in adult patients with CF as add-on maintenance therapy.[9] Mannitol DPI 400 mg twice daily demonstrated improvements over the control (inhaled mannitol 50 mg twice daily) with a mean change in baseline FEV_1 ranging from 51-68 mL.[9] Mannitol DPI is associated with bronchospasm and all patients should undergo a tolerance test, under supervision, before using for maintenance therapy. Due to the risk versus benefit, mannitol DPI is considered a second-line therapy for patients unable to tolerate other mucolytics.
- Two new FDA safety alerts have been issued since the last review. Updated labeling reflects a new warning for anaphylaxis and hypersensitivity reactions with inhaled amikacin. A warning was added for inhaled tobramycin for total, irreversible, bilateral congenital deafness in pediatric patients whose mothers received an aminoglycoside (streptomycin) during pregnancy,.[10,11]

Recommendations:
- Maintain inhaled mannitol as non-preferred on the preferred drug list (PDL). No changes to the PDL are warranted based on the current review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The last review of the inhaled CF agents was in January of 2016. There was insufficient direct comparative evidence between inhaled tobramycin and inhaled aztreonam for *P. aeruginosa.* After executive session the committee recommended that Kitabis Pak be preferred and TOBI, TOBI Podhaler and generic tobramycin be non-preferred.
- There were 33 claims for inhaled CF therapies quarter 2 of 2021.

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** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, 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:

<u>Cochrane – Inhaled Mannitol for Cystic Fibrosis</u>
The focus of a 2020 Cochrane review was the use of inhaled mannitol in adults and children with CF.[1] The main outcomes were respiratory function, quality of life and harms associated with treatment. A literature search ending December 2019 yielded 6 trials (n=784). Overall risk of bias was deemed low except for the requirement that all participants pass a mannitol screening test before being enrolled in the trial. Additionally, all trials were funded by the drug manufacturer. Trial durations were from 12 days to 6 months. Mannitol was compared to control (low-dose mannitol or non-respirable mannitol) in 5 trials and compared to dornase alfa in the remaining trial.[1] Two trials had additional 6-month, open-label extensions.

Results from 2 large trials were pooled (**Table 1**), but the other trials did not have outcomes that allowed for pooled assessment. Improvements in lung function parameters with mannitol 400 mg were demonstrated in patients regardless of concomitant use of dornase alfa. For the secondary outcome of pulmonary exacerbations, mannitol 400 mg was more effective than control based on the results of 2 pooled studies (relative risk [RR] 0.71; 95% CI, 0.51 to 0.98, P=0.04). One trial (n=28) evaluated the comparison between mannitol versus dornase alfa versus mannitol plus dornase alfa but did not find a difference between the groups based on very low quality evidence. A subgroup analysis found age did not have an effect on treatment efficacy. There was moderate quality of evidence of no difference in the incidence of mild, moderate or severe adverse reactions between inhaled mannitol 400 mg and control. Common adverse reactions in both groups included cough, hemoptysis, bronchospasm, pharyngeal pain and post-tussive vomiting.[1] The evidence for mannitol compared to non-respirable mannitol control (inpatient and outpatient) was very low or low quality, and therefore findings will not be presented in detail.

Table 1. Results for Inhaled Mannitol use in Patients with Cystic Fibrosis (Pooled results from 2 Trials [n=600] at 6 months)[1]

Outcome	Results	Quality of Evidence	Interpretation
Change from baseline in HRQoL	No difference between groups for age-appropriate versions of the CFQ-R questionnaire (multiple domains) Respiratory: mannitol 400 mg vs. control*: MD -0.99 (95% CI -4.50 to 2.52; p=0.58)	Low	*No difference in HRQoL found based on CFQ-R respiratory domain.*
Change from baseline in FEV_1 mL	mannitol 400 mg vs. control*: MD 86.5 mL (95% CI, 45.2 to 127.9 mL; p<0.00001)	Moderate	*Mannitol 400 mg improved lung function based on FEV_1 vs. control.*
Change from baseline in lung function FEV_1% predicted	mannitol 400 mg vs. control*: MD 3.89% (95% CI, 1.69% to 6.08%; P=0.0005)	Moderate	*Mannitol 400 mg improved lung function based on FEV_1% predicted vs. control.*
Change from baseline in FVC mL	mannitol 400 mg vs. control*: MD 102.17 mL (95% CI, 48.40 to 155.94 mL; p=0.00002)	Moderate	*Mannitol 400 mg improved lung function based on FVC vs. control.*
Change from baseline in FEF_{25-75} mL/s	mannitol 400 mg vs. control*: MD 42.67 mL (95% CI, -28.07 to 113.42 mL; p=0.24)	Moderate	*No difference lung function found based on FEF_{25-75}.*
Key: *Control = mannitol 50 mg. Abbreviations: CFQ-R – Cystic Fibrosis Questionnaire-Revised version; FEF_{25-75}- mild expiratory flow; FEV_1 – forced expiratory volume at 1 second; FVC – forced vital capacity; HRQoL – health-related quality of life; MD – mean difference; NA – not applicable; HRQL – health related quality of life			

Only patients who tolerated mannitol were eligible for the trials which may be a limitation of the applicability of evidence. There was insufficient evidence for clinically meaningful outcomes such as pulmonary exacerbations, hospitalizations, and symptom relief.

<u>Cochrane – Dornase Alfa for Cystic Fibrosis</u>

The effect of dornase alfa on morbidity and mortality outcomes in participants with CF was the focus of a 2021 Cochrane review.[2] Nineteen trials were identified which included 2565 participants, comprised of adults (4 trials) and children (4 trials) and 11 trials comprised of adults and children.[2] Dornase alfa was compared to placebo and other mucolytic therapies (e.g., hypertonic saline, mannitol). Trial durations lasted from 6 days to 3 years. The author determined that there was high risk or unclear risk of bias in at least one risk of bias domain for the included trials. No trial reported mortality outcomes; primary outcomes included changes in lung function, pulmonary exacerbations and changes in quality of life.

Results were not pooled for most findings, as most outcomes only had results from one trial or there was too much heterogeneity between the trials to pool results. Results for outcomes which are based on moderate to high quality evidence are presented in **Table 2**.[2] Comparisons of dornase alfa to placebo did not demonstrate quality of life differences based on the Cystic Fibrosis Questionnaire-Revised version [CFQ-R]. There was evidence from one study in children that dornase alfa administered daily resulted in improved mean changes in FEV_1 (L), mean relative percentage of FVC (L), and mean relative percentage if quality of life scores compared to alternating days of dornase alfa (all low quality evidence).[2] No difference between dornase alfa and hypertonic saline was found on the number of pulmonary exacerbations at 3 months, but there was a benefit of dornase alfa over hypertonic saline for the mean relative percentage increase in FEV_1 (L) (MD 8.00; 95% CI, 2.00 to 14.00) based on low quality evidence.[2] In children, a comparison of dornase alfa to mannitol (up to 475 mg) could not demonstrate a statistical benefit of dornase alfa for changes in FEV1 (L) or FVC (L). More participants who received dornase alfa had pulmonary exacerbations compared to mannitol (RR 1.10; 95% CI, 0.25 to 4.84) (all low quality evidence).[2] In children, there were no differences in most outcomes between dornase alfa plus mannitol compared to dornase alfa alone based on low quality of evidence. Fewer participants experienced a pulmonary exacerbation who received dornase alfa alone compared to dornase alfa plus mannitol (RR 0.55; 95% CI, 0.16 to 1.92) (very low quality evidence).[2] Common adverse events with dornase alfa included voice alteration and rash.

Table 2. Effects of Dornase Alfa Compared to Placebo in Participants with Cystic Fibrosis[2]

Outcome	Results	Quality of Evidence	Comments
Relative mean percentage change in FEV_1 % predicted at 3 months	MD 7.30% (95% CI, 4.04 to 10.56); p<0.0001	Moderate	Dornase alfa was more effective in improving FEV_1 % predicted compared to placebo
Relative mean percentage change in FEV_1 % predicted at 6 months	MD 5.80% (95% CI, 3.99 to 7.61); p<0.00001	High	Dornase alfa was more effective in improving FEV_1 % predicted compared to placebo
Relative mean percentage change in FVC % predicted at 3 months	MD 5.10% (95% CI, 1.23 to 8.97); p=0.001	Moderate	Dornase alfa was more effective in improving FVC % predicted compared to placebo
Relative mean percentage change in FVC % predicted at 6 months (once daily)	MD 3.80% (95% CI, 2.62 to 4.98): p<0.00001	High	Dornase alfa was more effective in improving FVC % predicted compared to placebo
Number of people experiencing pulmonary exacerbations	RR 0.78 (95% CI, 0.62 to 0.96); p=0.02	Moderate	Dornase alfa was more effective reducing exacerbations compared to placebo

Abbreviations: CI – confidence interval; FEV_1 – forced expiratory volume at 1 second; FVC – forced vital capacity; MD – mean difference; RR – relative risk.

<u>Cochrane – Antibiotic Strategies for Eradicating *Pseudomonas Aeruginosa* in People with Cystic Fibrosis</u>

A 2017 Cochrane review evaluated at the evidence for early treatment of *P. aeruginosa* infection in children and adults with CF.[3] Specific outcomes of interest were: superiority of a particular antibiotic, organism eradication, delay in the onset of chronic infection, and clinical improvement. Combination treatments of inhaled, oral or IV antibiotics were compared to placebo, usual treatment or other combinations of antibiotics therapies (e.g., inhaled, oral or IV). Seven trials

(n=744) met inclusion criteria with durations lasting from 28 days to 27 months.[3] Only 2 trials included adult patients. Many of the trials enrolled a small number of patients and 3 trials were over 10 years old. Much of the evidence was considered to be of low or very low quality and all trials had unclear risk of bias in some domains.

Two trials evaluated the use of inhaled tobramycin compared to placebo. For the outcome of microbiological eradication from the respiratory secretions at 2 months, tobramycin was more effective than placebo odds ratio (OR) 0.15 (95% CI, 0.03 to 0.65) (very low quality of evidence).[3] Low quality of evidence from 1 trial demonstrated no difference between inhaled tobramycin plus oral ciprofloxacin compared to inhaled colistin plus oral ciprofloxacin for eradication of *P. aeruginosa* (OR 1.28; 95% CI, 0.72 to 2.29; p-value not reported).[3] There was moderate quality evidence of more adverse events with inhaled tobramycin plus oral ciprofloxacin compared to inhaled colistin plus oral ciprofloxacin, 18% vs. 16%, respectively.[3] One randomized trial found moderate quality evidence that cycled based inhaled tobramycin was more effective than culture-based inhaled tobramycin for the outcome of *P. aeruginosa* eradication from the respiratory tract (OR 0.51; 95% CI, 0.31 to 0.82; p-value not reported). For the outcome of growth and nutritional status, based on weight and height, no differences were found between groups (moderate quality evidence). There was no difference in the amount of infective pulmonary exacerbation between cycled based inhaled tobramycin and culture-based inhaled tobramycin (OR 0.75; 95% CI, 0.48 to 1.17; p-value not reported).[3] There was no difference in the incidence of adverse events between groups. There was moderate quality evidence that there was no difference in eradication of *P. aeruginosa* from the respiratory tract between cycled and culture-based inhaled tobramycin therapy plus placebo compared to ciprofloxacin added to cycled and culture-based inhaled tobramycin (OR 0.89; 95% CI, 0.55 to 1.44) (moderate quality of evidence).[3] There was no difference between groups on growth and nutritional status, frequency of infective pulmonary exacerbations, number of other micro-organisms isolated from the respiratory tract or adverse events.

Limitations to the evidence are the inclusion of mostly children in the trials and imprecision of the results. Additionally, a majority of evidence was graded as low or very low quality also adding to the inability to draw strong conclusions.

<u>Cochrane – Treatments for Preventing Recurrence of Infection with *Pseudomonas Aeruginosa* in People with Cystic Fibrosis</u>

A 2019 Cochrane review evaluated secondary prevention strategies, including inhaled antibiotics, on the incidence of freedom from *P. aeruginosa* infection following eradication.[4] Only 1 trial (n=306) met inclusion criteria, with analysis of only 253 participants since the other participants did not have eradication of *P. aeruginosa* infection following an initial 28-day course of inhaled tobramycin therapy.[4] Participants had a CF diagnosis, were 51% female, and had a mean age of 6 years. Median follow-up was 494 days. The trial compared cycled therapy, which was inhaled tobramycin solution 300 mg twice daily every 3 months without regard to culture results, versus culture-based therapy, which was inhaled tobramycin solution 300 mg twice daily only in the 3-month period that culture results were positive for *P. aeruginosa.* Fifty-three percent of participants in each group also underwent a second comparison with the addition of oral ciprofloxacin 15-20 mg/kg/dose twice daily for 14 days to each of the previously described regimens.[4] Important outcomes were time to next isolation of *P. aeruginosa,* FEV_1 changes and pulmonary exacerbations.

The trial was at low risk of bias except that the study was funded by the manufacturer. One set of results were presented, irrespective of whether the participants also received ciprofloxacin. There was moderate quality of evidence that culture-based therapy was more likely to have a recurrence by their final study visit (up to 563 days) compared to those in the cycled therapy (HR 2.04; 95% CI, 1.28 to 3.26; p=0).[4] There was no difference found in the rate of pulmonary exacerbations between groups based on moderate quality evidence and no difference found in FEV_1 changes based on very low quality of evidence. There was also no difference found between the groups in the incidences of severe adverse reactions or emergence of novel bacteria.

The high enrollment of children limits the applicability to adult CF populations. There was insufficient evidence on time to development of chronic *P. aeruginosa* or quality of life outcomes.

Cochrane – Inhaled Antibiotics for Pulmonary Exacerbations in Cystic Fibrosis

A 2018 Cochrane review evaluated the use of inhaled antibiotics in adults and children with CF.[5] One hundred sixty-seven participants from 4 trials were included. Two trials compared inhaled antibiotics to IV antibiotics and two trials compared inhaled antibiotics plus IV antibiotics to IV antibiotics alone. Inhaled antibiotics studied were tobramycin, carbenicillin, ceftazidime and amikacin and IV antibiotics were ticarcillin, tobramycin and ceftazidime.[5] The outcomes evaluated quality of life, survival and reduced time off of school or work. High risk of bias was present for all included trials.

Evidence for all outcomes were considered very low quality. One small trial (n=18) demonstrated perceived improvement in quality of life for both inhaled antibiotic and IV antibiotic groups.[5] There was no difference found in lung function in the trials that compared inhaled antibiotics versus IV antibiotics or in the trials that compared inhaled antibiotics plus IV antibiotics versus IV antibiotics alone.

There was insufficient evidence to conclude if inhaled antibiotics, alone or in combination with IV antibiotics, are more effective than IV antibiotics alone at improving lung function or quality of life.

Cochrane – Nebulised Hypertonic Saline for Cystic Fibrosis

A Cochrane review evaluated the evidence that compared hypertonic saline with other mucolytic therapies or placebo in participants with CF.[6] Seventeen trials enrolling 966 participants were included. Participants ranged from 4 months to 63 years of age. Hypertonic saline (3% to 7% given twice daily) was compared to placebo and the following active treatments: rhDNase, amiloride, and mannitol.[6] All trials were considered to be at high risk of bias due to allocation concealment issues. Outcomes evaluated were lung function (e.g., FEV_1 % predicted) lung clearance index, measures of sputum clearance, and pulmonary exacerbations. Due to heterogeneity, some of the results were not pooled.

The evidence for all outcomes was low to very low quality. In placebo-controlled trials, hypertonic saline was more effective at increasing the mean change from baseline of the FEV_1 by 3.44% (95% CI, 0.67 to 6.21), with no change in lung clearance index between the groups measured at 4 weeks.[6] There was insufficient evidence to compare adverse events. Four trials demonstrated a higher rate of sputum clearance with hypertonic saline compared to placebo. One trial in patients with acute exacerbation of lung disease found hypertonic saline improved short-term lung function by 5.10% versus placebo (95% CI, -14.67% to 24.87%).[6]

One trial found that rhDNase was more effective than hypertonic saline at increasing FEV1 %-predicted in patients with moderate to severe lung disease (MD 8.00%; 95% CI, 2.00 to 14.00).[6] Other active treatment comparisons found no difference and were considered very low-quality evidence.

After review, 9 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).[12–19]

New Guidelines:

NICE – Cystic Fibrosis: Diagnosis and Management

The 2017 NICE guideline covered the management of CF.[7] The guideline includes recommendations from 2 previously published guidelines on mannitol DPI, colistimethate sodium and tobramycin DPI for the treatment of *P aeruginosa*. Updated recommendations for mucoactive agents and antibiotics are discussed below.

Recommendations for Mucoactive Agents:

- Mucoactive therapies should be offered to people with CF who have clinical evidence of lung disease; specifically rhDNase (dornase alfa; recombinant human deoxcyribonuclease) is recommended as a first-line treatment option.[7]
- If there is evidence of an inadequate response to rhDNase based on lung function or clinical evaluation, then combination therapy with rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone should be considered.[7]
- Mannitol DPI for children and young people should be considered if they are unable to take rhDNase and hypertonic sodium chloride due to intolerance or due to suboptimal response.[7]
- Mannitol DPI for adults is recommended for individuals unable to tolerate rhDNase, have rapidly declining lung function (FEV_1 decline is 2% or greater annually), or who are not candidates for the use of other osmotic agents.[7]

Recommendations for the treatment of pulmonary infection, including oral and inhaled antibiotic therapies:

- Treatment of an active *Staphylococcus aureus* (*S. aureus)* infection should be with oral anti-*S. aureus* agent.[7]
- Treatment of *P. aeruginosa* should consist of oral or IV antibiotics in combination with an inhaled antibiotic.
    - If eradication is not obtained despite treatment, the use of sustained treatment with an inhaled antibiotic should be considered.[7]
    - A combination of an oral antibiotic or combination of 2 IV antibiotics should be considered depending on infection severity of *P. aeruginosa*.
- Patients with chronic *Burkholderia cepacian* complex infection and declining pulmonary status should be considered for sustained treatment with an inhaled antibiotic for infection suppression (antibiotic choice should be based on advice from microbiological specialist).[7]
- *Haemophilus influenzae* should be treated with oral or IV antibiotic depending on infection severity.[7]
- Patients with *Aspergillus fumigatus* with declining pulmonary status should be treated with an antifungal agent determined by a microbiological specialist.
- Patients with repeated pulmonary exacerbations or deteriorating lung function should be considered for long-term treatment with azithromycin at an immunomodulatory dose (dose that is less than the minimum inhibitory dose). If pulmonary exacerbations and deteriorating lung function persist with long-term azithromycin, then oral corticosteroids should be considered and azithromycin should be discontinued.[7]

Recommendations for tobramycin DPI:

- Use in patients with chronic *P. aeruginosa* pulmonary infection if nebulized tobramycin is considered appropriate.[7]

<u>NICE – Cystic Fibrosis Quality Standards 2018</u>

NICE updated its recommendations for quality standards CF in 2018. Quality standards for drug therapy for people with CF were provided for those who are candidates for a mucoactive agent or if they were infected with *P.aeruginosa*.[8] The following quality statements are provided:

- Patients with CF and chronic *P. aeruginosa* should have sustained inhaled antibiotic therapy.[8] *P. aeruginosa* can cause worsening signs and symptoms and reduced lung function in patients with chronic infection (3 or more isolates in the preceding 12 months). Inhaled antibiotic use on a chronic basis can help maintain lung function and quality of life.

- Patients with CF and have clinical evidence of lung disease should be prescribed rhDNase (e.g., dornase alfa) as a first-line mucoactive agent.[8] Mucoactive agents help to clear the sticky mucus that accumulates in the lungs of patients with CF, which predisposes them to infection. Evidence has shown that mucoactive therapies help to maintain lung function and prevent infection.

After review, 3 guidelines were excluded due to poor quality.[20,21,22]

New Indications:

Mannitol Inhalation Powder (Bronchitol®): In October 2020, the FDA approved mannitol DPI as add-on maintenance therapy to improve pulmonary function in adult patients with CF who are 18 years and older.[9] All adult patients should pass a tolerance test using inhaled mannitol. The dose is 10 capsules (400 mg) twice daily by oral inhalation, with the second dose taken 2-3 hours before bedtime.[9]

The Bronchitol® tolerance test (BTT) is required because of the risk of bronchospasm, which can be severe.[9] The BTT must be administered under the supervision of a healthcare provider who is able to treat severe bronchoconstriction. Patients who do not pass the BTT should not be prescribed inhaled mannitol. Patients should premedicate with a short-acting bronchodilator before each administration of inhaled mannitol. Bronchospasms may also occur with maintenance use of inhaled mannitol.[9] If bronchospasms occur, patients should discontinue treatment with inhaled mannitol and treat with a short-acting bronchodilator.

Inhaled mannitol was studied in 3, 26-week, double-blind, randomized controlled trials in children and adult patients with CF.[9] The trials differed by age and FEV_1: patients 18 years of age or older with baseline FEV_1 >40% to <90% of predicted; 6 years of age or older with baseline $FEV_1 \geq 30\%$ to <90% predicted; or patients 6 years of age or older with baseline $FEV_1 \geq 40\%$ to <90% of predicted.[9] Standard of care CF therapies (e.g., bronchodilators, inhaled antibiotics, and dornase alfa) were allowed except inhaled hypertonic saline was not permitted. Trials studied twice daily inhaled mannitol 400 mg versus control (50 mg inhaled mannitol), premedicating with a short-acting bronchodilator (e.g., albuterol or equivalent).[9]

The primary outcome was mean change in pre-dose FEV_1 (mL) from baseline. In the first trial (n=423), the mean change in pre-dose FEV_1 between inhaled mannitol and control was 51 mL (95% CI, 6 to 97 mL; p=0.028).[9] Similar findings were demonstrated in the second and third trial, with a mean change favoring inhaled mannitol versus control (68 mL; 95% CI, 24 to 113 mL, and 52 mL; 95% CI, -3 to 107 mL, respectively).[9] The second and third trials included patients under the age of 18 years; however, inhaled mannitol is not indicated in this population.

Common adverse events noted in clinical trials included cough, hemoptysis, oropharyngeal pain, vomiting, bacteria in sputum, pyrexia and arthralgia. Patients who experience hemoptysis with the use of inhaled mannitol should discontinue use.[9]

New FDA Safety Alerts:

Table 3. 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)
Amikacin[10]	Arikayce Kit	March 2020	Warnings	Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported.
Tobramycin[11]	NA	April 2020	Warnings	Aminoglycosides, including tobramycin, have been associated with several reports of total, irreversible, bilateral congenital deafness in pediatric patients whose mothers received the aminoglycoside, streptomycin. Patients should be informed of hazard to fetus.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
dornase alfa	PULMOZYME	SOLUTION	Y
sodium chloride for inhalation	SODIUM CHLORIDE	VIAL-NEB	Y
tobramycin/nebulizer	KITABIS PAK	AMPUL-NEB	Y
tobramycin/nebulizer	TOBRAMYCIN	AMPUL-NEB	Y
amikacin liposomal/neb.accessr	ARIKAYCE	VIAL-NEB	N
aztreonam lysine	CAYSTON	VIAL-NEB	N
mannitol	BRONCHITOL	CAP W/DEV	N
tobramycin	BETHKIS	AMPUL-NEB	N
tobramycin	TOBRAMYCIN	AMPUL-NEB	N
tobramycin	TOBI PODHALER	CAP W/DEV	N
tobramycin	TOBI PODHALER	CAPSULE	N
tobramycin in 0.225% sod chlor	TOBI	AMPUL-NEB	N
tobramycin in 0.225% sod chlor	TOBRAMYCIN	AMPUL-NEB	N

Appendix 2: New Comparative Clinical Trials

A total of 334 citations were manually reviewed from the initial literature search. After further review, 333 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Flume, et al[23] MC, DB, PG, RCT 26 weeks	Inhaled mannitol 400 mg twice daily Vs. Inhaled mannitol 50 mg twice daily (control) Maintenance antibiotic therapy and rhDNase therapy was permitted	Adult with CF, FEV_1 40% to 90% predicted (n=423)	FEV_1 averaged over the 26-week treatment period	Mannitol 400 mg: 63 mL Mannitol 50 mg: 8 mL MD 54 mL (95% CI, 8 to 100 mL) P=0.020	Randomization was appropriate and double-dummy design adequately masked treatment. Limitations to the study include the averaging of FEV_1 over 26 weeks which increases the magnitude of benefit. Change from baseline FEV_1 at 26 weeks was not statistically different between groups. The mean change from baseline in FVC average over 26 weeks was not statistically different between groups. Ninety-seven percent of patients were White which significantly reduces applicability to real world populations.

Abbreviations: CF = cystic fibrosis; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MC = multi-center; MD = mean difference; PG = parallel group; RCT = randomized clinical trial; rhDNase = recombinant human deoxyribonuclease

Appendix 3: Abstracts of Comparative Clinical Trials

Efficacy and safety of inhaled dry-powder mannitol in adults with cystic fibrosis: An international, randomized controlled study
Flume P, Amelina E, Daines C, Charlton B, et al
Abstract
Background: Mannitol is a mucoactive hyperosmotic agent used as add-on therapy in patients with cystic fibrosis (CF), administered twice-daily (BID) via a small, portable, breath-actuated dry-powder inhaler. This study was conducted to provide confirmatory evidence of mannitol's efficacy and safety in adults.
Methods: This multicenter, double-blind, randomized, parallel-group, controlled clinical trial recruited adults (aged ≥18 years) with CF, and forced expiratory volume in 1 second (FEV1) 40-90% predicted. Subjects received either mannitol 400 mg or mannitol 50 mg (control), BID via dry-powder inhaler for 26 weeks. Primary endpoint: FEV1 averaged over the 26-week treatment period.
Results: Of 423 subjects randomized (209 or 214 receiving mannitol 400 mg BID or control, respectively), 373 (88.2%) completed the study, with a similar proportion completing in the two groups. For FEV1 averaged over 26 weeks, mannitol 400 mg BID was statistically superior to control (adjusted mean difference 54 mL [95% CI 8, 100 mL]; p = 0.020). This was supported by sensitivity analyses of the primary endpoint, and by observed improvements in secondary pulmonary function endpoints (eg, absolute adjusted mean difference in percent predicted FEV1 averaged over 26 weeks 1.21% [0.07%, 2.36%]; p = 0.037). Adverse events were mainly mild or moderate in severity, with treatment-related adverse events in 15.5 and 12.2% of subjects receiving mannitol 400 mg BID and control, respectively.
Conclusions: In adults with CF, mannitol 400 mg BID inhaled as a dry-powder statistically significantly improved lung function (FEV1) compared with control, with this improvement supported by sensitivity analyses and secondary pulmonary function endpoints. Mannitol had a good overall safety and tolerability profile. ClinicalTrials.gov: NCT02134353.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to September 03, 2021

Search Strategy:

#	Searches	Results
1	dornase alfa.mp.	259
2	tobramycin.mp.	8144
3	amikacin.mp.	11037
4	sodium chloride.mp. or Sodium Chloride/	81324
5	aztreonam.mp. or Aztreonam/	3566
6	Mannitol/ or mannitol.mp.	24070
7	1 or 2 or 3 or 4 or 5 or 6	124119
8	limit 7 to (english language and humans and yr="2015 -Current")	8096
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	334

Appendix 5: Key Inclusion Criteria

Population	Adults and children with cystic fibrosis
Intervention	Inhaled drugs for cystic fibrosis
Comparator	Placebo or active treatments
Outcomes	Mortality, improvement in lung function, improvement in symptoms, organism eradication, quality of life
Timing	As needed and scheduled maintenance therapy
Setting	Outpatient

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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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
asciminib	SCEMBLIX
mobecertinib	EXKIVITY
tisotumab vedotin-tftv	TIVDAK

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 11/01/2021)
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
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT

Generic Name	Brand Name
sipuleucel-T/lactated ringers	PROVENGE
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
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

Generic Name	Brand Name
ziv-aflibercept	ZALTRAP

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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
Avacopan	TAVNEOS
Maralixibat	LIVMARLI
Odevixibat	BYLVAY

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 years	30 mg (three 10 mg capsules) twice daily, with food	Baseline Monitoring • Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin) • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 weeks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 months TIO ≥ 2 years	Pediatric <18 years: Initial (administered SC every 2 weeks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg	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

			Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max 2 mg/kg or 180mg every 2 weeks)	<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 (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 years	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, ~~aspartate aminotransferase (~~AST~~)~~, ~~alanine aminotransferase (~~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 years	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 weeks) Initial: 0.4 mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 weeks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥ 1 year 0.9 mg/kg	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 years	2.5 mg/kg monthly	<u>Baseline and ongoing monitoring</u> • Liver function tests • blood homocysteine levels
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 months AND ≥0.39 m^2 body surface area	• 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	<u>Baseline and ongoing monitoring</u> • 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	Adult and pediatric patients	**<10 kg** <u>Loading:</u> 6 mg/kg once/month for 3 doses <u>Maintenance:</u> 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 Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hg <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hg <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 years	Initial: 1 mg/kg subcutaneously Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia Max dose of 1.75 mg/kg every 3 weeks 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 weeks 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 weeks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 1 year	Initial: 190 mcg/kg once daily, 30 min before first meal of day	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

			Goal: 390 mcg/kg once daily after 1 week on initial dose, as tolerated	
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 months	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 (hypoplasminogenemia)	N/A	6.6 mg/kg body weight given intravenously 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 weeks with ongoing therapy • CBC (bleeding)

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.

Approval Criteria		
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
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: 12/21 (SF); 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

ProDUR Report for July through September 2021
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	0	0	0	0	0.00%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	2,006	387	0	1,618	1.74%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	5,748	1,304	6	4,437	4.97%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	75,853	13,086	25	62,736	65.61%	**17.3%**
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	22,588	5,412	3	17,165	19.54%	**N/A**
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	599	120	0	478	0.52%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	4	2	0	0	0.00%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	805	229	0	576	0.70%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	397	116	0	281	0.34%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	14	13	0	1	0.01%	**92.9%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,597	1,977	0	5,616	6.57%	**N/A**
		Totals	**115,611**	**22,646**	**34**	**92,908**	**100.00%**	**19.6%**

ProDUR Report for July through September 2021
Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,437	222	1,215	13,016	11.6%	14.4%
ER	Lorazepam	304	73	231	11,847	2.6%	24.0%
ER	Alprazolam	157	28	129	7,146	2.2%	17.8%
ER	Diazepam	100	21	79	4,003	2.5%	21.0%
ER	Buspirone (Buspar)	2,890	424	2,466	30,340	9.5%	14.7%
ER	Lamictal (Lamotrigine)	4,889	910	3,978	39,750	12.3%	18.6%
ER	Seroquel (Quetiapine)	3,626	737	2,889	28,035	12.9%	20.3%
ER	Zyprexa (Olanzapine)	2,196	418	1,778	17,655	12.4%	19.0%
ER	Risperdal (Risperidone)	1,659	332	1,327	12,627	13.1%	20.0%
ER	Abilify (Aripiprazole)	2,863	448	2,415	24,838	11.5%	15.6%
ER	Wellbutrin (Bupropion)	2,695	405	2,190	62,509	4.3%	15.0%
ER	Suboxone (Buprenorphine/Naloxone)	31	9	22	1,632	1.9%	29.0%
ER	Zoloft (Sertraline)	2,817	516	2,301	67,965	4.1%	18.3%
ER	Prozac (Fluoxetine)	2,250	378	1,872	49,024	4.6%	16.8%
ER	Lexapro (Escitalopram)	2,031	345	1,686	45,227	4.5%	17.0%
ER	Celexa (Citalopram)	779	102	677	24,842	3.1%	13.1%
ER	Trazodone	2,173	423	1,750	53,221	4.1%	19.5%
ER	Cymbalta (Duloxetine)	1,971	401	1,569	41,645	4.7%	20.3%
ER	Intuniv (Guanfacine)	681	106	575	11,115	6.1%	15.6%

ProDUR Report for July through September 2021
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	July	3,847	200	288	806	8	2,262	122	0	161
ER	August	3,290	128	244	728	4	1,987	108	0	91
ER	September	3,569	164	266	767	6	2,125	115	0	126
	Total =	**10,706**	**492**	**798**	**2,301**	**18**	**6,374**	**345**	**0**	**378**
	Percentage of total overrides =		**4.6%**	**7.5%**	**21.5%**	**0.2%**	**59.5%**	**3.2%**	**0.0%**	**3.5%**

ProDUR Report for July through September 2021			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
Jul-21	ER	14	$4,566.42
Jul-21	ID	3	$258.27
		July Savings =	**$4,824.69**
Aug-21	DC	1	$140.69
Aug-21	ER	31	$5,679.68
Aug-21	ID	10	$1,881.35
Aug-21	LR	1	$68.41
Aug-21	TD	1	$102.69
		August Savings =	**$7,872.82**
Sep-21	DC	1	$27.99
Sep-21	DD	4	$373.00
Sep-21	ER	43	$7,248.04
Sep-21	ID	20	$3,471.86
Sep-21	LD	1	$848.48
Sep-21	PG	1	$30.99
Sep-21	TD	3	$319.65
		September Savings =	**$12,320.01**
		Total 3Q2021 Savings =	**$25,017.52**

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Desvenlafaxine Salt Formulations	Unique Prescribers Identified		52	48	80
		Unique Patients Identified		53	48	84
		Total Faxes Successfully Sent		44	27	61
		Prescriptions Changed to Recommended Within 6 Months of Intervention		27	24	21
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$35,420	$17,136	$7,006
	Fluoxetine Tabs to Caps	Unique Prescribers Identified	23			
		Unique Patients Identified	23			
		Total Faxes Successfully Sent	15			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	7			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$783			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	146	293	210	235
		Unique Patients Identified	147	300	215	238
		Total Faxes Successfully Sent	99	210	101	131
		Prescriptions Changed to Recommended Within 6 Months of Intervention	84	133	91	64
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$103,687	$112,232	$49,805	$11,356

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	51	50	77	80
		Total Faxes Successfully Sent	10	17	11	9
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	9	5	1
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	11	2		1
		Prescriptions Unchanged after 3 Months of Fax Sent	28	29	68	
		Safety Monitoring Profiles Identified	7	10	3	6
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	($12,767)	$19,950	$11,423	$809

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	936	606	878	820
		High risk patients identified	13	6	7	3
		Prescribers successfully notified	13	6	7	3
		Patients with change in antipsychotic drug in following 90 days	2			
		Patients with continued antipsychotic therapy in the following 90 days	8	6	7	2
		Patients with discontinuation of antipsychotic therapy in the following 90 days	2			

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	69	66	52	57
		Total prescribers identified	68	66	52	57
		Prescribers successfully notified	68	66	46	54
		Patients with claims for the same antipsychotic within the next 90 days	37	36	25	22
		Patients with claims for a different antipsychotic within the next 90 days	5	4	3	2

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Foster care children under age 12 on antipsychotic	RetroDUR_Profiles Reviewed	75	159	59	68
	Foster care children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	18	27	12	25
	Foster care children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	113	237	134	132
	Foster care children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	17	31	21	25
	High Risk Patients - Bipolar	RetroDUR_Profiles Reviewed				9
		RetroDUR_Letters Sent To Providers				5
	High Risk Patients - Mental Health	RetroDUR_Profiles Reviewed				50
		RetroDUR_Letters Sent To Providers				62
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed	10		10	22
		RetroDUR_Letters Sent To Providers	4		4	6
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed			1	
		RetroDUR_Letters Sent To Providers			2	
	Lock-In	RetroDUR_Profiles Reviewed	14	20	25	5
		RetroDUR_Letters Sent To Providers	2	1	1	
		Locked In	1	1	1	0
	Polypharmacy	RetroDUR_Profiles Reviewed	27	16	26	31
		RetroDUR_Letters Sent To Providers	6	3	4	15

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	120	123	122	104
		Total prescribers identified	119	123	121	104
		Prescribers successfully notified	112	110	99	93
		Patients with discontinuation of therapy within next 90 days	29	25	19	42
		Patients with new prescription for naloxone within next 90 days	4	4	4	
		Average number of sedative drugs dispensed within next 90 days	24	24	24	12
		Average number of sedative prescribers writing prescriptions in next 90 days	24	24	24	12
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified		62	75	56
		Patients with a paid claim for the drug (based on HSN) within 14 days		37	50	40
		Patients without a paid claim within 14 days		25	25	10
	ICS/LABA	ICS/LABA Denials	26	21	36	29
		Disqualified	6	6	11	9
		Faxes Sent	1	2		1
		Fax Sent - SABA				1
		Fax Sent - Combination Inhaler	1	1		
		No Subsequent Pulmonary Claims		1		
	Oncology Denials	Total patients identified	1	3		2
		Total prescribers identified	1	3		2
		Prescribers successfully notified	1	1		1
		Patients with claims for the same drug within the next 90 days	1	2		
		Patients with claims for any oncology agent within the next 90 days	1	2		1

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	TCAs in Children	TCA Denials in Children	26	21	36	27
		Total patients identified	10	6	13	9
		Total prescribers identified	10	6	13	9
		Prescribers successfully notified	7	1	5	6
		Patients with claims for a TCA within the next 90 days	2	1	1	4
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1		

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COVID-19 Vaccine Update

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To date, three COVID-19 vaccines have received Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) for administration to the American population. Safety and efficacy for the two messenger ribonucleic acid (mRNA) vaccines were reviewed in the January 2021 edition of the Oregon State Drug Review.[1] Vaccines approved or currently being studied are presented in **Table 1.** As the mRNA vaccines became available in the United States (US), COVID-19 variants from the United Kingdom, South Africa, and Brazil emerged in North America. The mRNA vaccines were studied when virus variants were not widely circulating. This newsletter will review the evidence supporting the efficacy of the single-dose viral vector Janssen-Johnson & Johnson vaccine in preventing moderate to severe COVID-19 and address ongoing concerns related to COVID-19 vaccinations.

Table 1. COVID-19 Vaccines Authorized or Under Investigation in Phase 2 and 3 Trials[2]

Vaccine Manufacturer	Mechanism	Age	Dosing Schedule	EUA Status
Pfizer-BioNTech BNT162b2	mRNA	≥16 yo	0.3 mL IM for 2 doses (Days 0, 21)	Authorized 12/11/20
Moderna mRNA-1273	mRNA	≥18 yo	0.5mL IM for 2 doses (Days 0, 28)	Authorized 12/20/20
Janssen-Johnson & Johnson Ad26.COV2.S	Viral Vector	≥18 yo	0.5 ml IM for 1 dose (Day 0)	Authorized 2/27/21
AstraZeneca-Oxford AZD1222	Viral Vector	N/A	2 doses (Days 0, 28)	Anticipated 2021
Novavax NVX-CoV2373	Protein Subunit	N/A	2 doses (Days 0, 21)	Anticipated 2021
Sanofi-GSK	Protein Subunit	N/A	2 doses (Days 0, 21)	Anticipated 2022

Abbreviations: EUA = Emergency Use Authorization; IM = intramuscular; mL = milliliters; mRNA = messenger RNA; N/A = Not Available; yo = years old

Janssen COVID-19 Vaccine

The Janssen COVID-19 vaccine received EUA for use in persons aged 18 years and older for the prevention of COVID-19 on February 27, 2021.[3] The Janssen COVID-19 vaccine is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine, encoding the stabilized prefusion spike glycoprotein of SARS-CoV-2.[3] While adenoviruses are relatively common, Ad26 has been modified for this product so that it cannot replicate in the human body to cause illness. After vaccination, the body can temporarily make the spike protein, which prompts an immune response against the SARS-CoV-2 virus. Viral vector vaccines have been studied since the 1970s. Two Ebola vaccines currently in use are both viral vector vaccines. The first of these vaccines was approved by the FDA in December 2019 following review of 12 clinical trials that included a total of 15,399 adults.[4] Viral vector vaccines have also been used in clinical trials against viruses that include the Zika virus, human immunodeficiency virus (HIV) and influenza viruses.

Immunization with the Janssen COVID-19 vaccine consists of a single 0.5-mL dose administered intramuscularly.[3] The vaccine may be stored refrigerated at 36° to 46° F (2° to 8°C) for up to 3 months. The Janssen vaccine was studied in geographic areas when COVID-19 virus variants were circulating, particularly in South Africa and Brazil.

The effectiveness data to support the Janssen COVID-19 vaccine EUA is based on results from an ongoing randomized, double-blind, placebo-controlled phase 3 study (ENSEMBLE) conducted in the US, South Africa, Brazil, Chile, Argentina, Columbia, Peru, and Mexico.[5] Adults (n=44,325) who did not have evidence of SARS-CoV-2 infection prior to receiving the vaccine were eligible for enrollment in the trial.[5] Participants were randomized 1:1 to receive vaccine (n=19,630) or saline placebo (n=19,691).[5] Subjects were followed for a median of eight weeks after vaccination. Overall, 58.7% of participants were White, 45.3% were Hispanic or Latino, 19.4% were Black or African American, 9.5% were American Indian or Alaska Native, 3.5% were Asian, 0.2% were Native Hawaiian or other Pacific Islander, and 5.6% were multiracial.[5] The median age of study participants was 52 years and 45% were female.[5] Demographic characteristics were similar among individuals who received the Janssen COVID-19 vaccine and those who received saline placebo.[5] Approximately 41% of enrolled patients had a least 1 coexisting condition.[5]

The co-primary endpoints for the ENSEMBLE trial were efficacy of a single dose of vaccine to prevent symptomatic, laboratory confirmed, moderate to severe/critical COVID-19 occurring 1) at least 14 days after vaccination and 2) at least 28 days after vaccination in study participants. Severe/critical COVID-19 was defined as: a severe systemic response requiring respiratory support, or evidence of shock, or significant organ damage, or admission to intensive care unit.[3] Results from the trial are presented in **Table 2.**

Table 2. ENSEMBLE Trial Results[5]

Outcome	Number of Cases (N=19,630) Vaccine	Number of Cases (N =19,691) Placebo
COVID-19 Cases 14 days post-vaccination	116 (0.6%)	348 (1.8%)
COVID-19 Cases 28 days post-vaccination	66 (0.3%)	193 (0.90%)
Hospitalization 14 days post-vaccination	2 (0.01%)	29 (0.14%)
Hospitalization 28 days post-vaccination	0	16 (0.08%)

Overall, the vaccine was approximately 66.9% [95% Confidence Interval (CI) 59.0 to 73.4] effective in preventing moderate COVID-19 occurring at least 14 days after vaccination and 66.1% (95% CI 55 to 74.8) effective in preventing moderate COVID-19 occurring at least 28 days after vaccination.[5] Additionally, the vaccine was approximately 76.7% (95% CI 54.6 to 89.1) effective in preventing severe/critical COVID-19 occurring at least 14 days after vaccination and 85.4% (95% CI 54.2 to 96.9) effective in preventing severe/critical COVID-19 occurring at least 28 days after vaccination.[5] Vaccine efficacy varied geographically and was highest in the US (74.4%) and lowest in South Africa (52%), where the B.1.351 variant dominated.[3] As of the primary analysis cutoff date of 1/22/21, there were no COVID-19-related deaths reported in the vaccine arm compared to 5 COVID-19-related deaths reported in the placebo arm.[5]

Safety Concerns

The safety subset population included 6,736 individuals. Geographically, the safety subset was limited to individuals from the US (51.4%), Brazil (38.5%) and South Africa (10.2%).[6] The most commonly reported side effects were local adverse events such as pain at the injection site (48.6%), and systemic adverse events including headache (38.9%), fatigue (38.2%), myalgia (33.2%) and nausea (14.2%).[5] Most of these side effects were mild to moderate in severity and lasted 1 to 2 days.[5] Overall, symptoms were more frequent in younger people than individuals aged over 60 years of age.[5]

Viral vector vaccines have been associated with rare, but serious thrombosis-thrombocytopenia syndrome (TTS) reported in the first 2 weeks after vaccine administration.[7] To date, 8 million doses of the Janssen vaccine have been administered in the U.S. and 15 cases of TTS have been reported.[7] Most cases of TTS reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal.[7] The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia, which is why heparin should be avoided in patients exhibiting symptoms of TTS after COVID-19 vaccination.[6] After a 10 day pause to investigate the possible link between the vaccine and TTS, the CDC approved resuming administration of the Janssen vaccine on Friday, April 25, 2021.[7] At this time, the available data suggest the chance of TTS occurring is very low, but the FDA and CDC will remain vigilant in continuing to investigate this risk.[7]

Health care providers should alert their patients to be aware of any symptoms of TTS, which include severe headache, vision changes such as blurry vision, extremity pain or swelling, chest pain, and shortness of breath. People should not be concerned about mild headaches and flu-like symptoms in the first few days after vaccination as these are commonly reported side effects. The Astra Zeneca vaccine has been associated with a similar hematologic disorder in European patients. The European Medicines Agency has determined the benefits of the AstraZeneca COVID-19 vaccine outweigh the risks. No reports of blood clots events have been reported with the mRNA vaccines manufactured by Pfizer and Moderna.

Comparative Vaccine Efficacy

The only way to accurately compare the effectiveness of vaccines is by direct comparison in head-to-head clinical trials, which did not occur for any of the COVID-19 vaccines. The clinical trials for these vaccines occurred in different geographic regions and at different points in time with varying incidence of COVID-19. In addition, the primary outcome for the mRNA vaccines was the efficacy in preventing symptomatic COVID-19 compared with placebo 7 days after the second dose (Pfizer) or 14 days after the second dose (Moderna). In contrast, the primary outcome for the Janssen vaccine stratified the severity of COVID-19 as moderate or severe disease and evaluated occurrence of infection 14 and 28 days post vaccination. All the COVID-19 vaccines the FDA has authorized for emergency use are at least 50% more effective than placebo in preventing COVID-19 (range 65 to 95%). According to FDA guidance, a vaccine with at least 50% efficacy would have a significant impact on disease, both at the individual and societal level.[8]

Vaccine Efficacy Against SARS-CoV-2 Variants

One reason SARS-CoV-2 variants are emerging is because relatively few people globally have been vaccinated.[9] Current COVID-19 vaccines are based on the SARS-CoV-2 spike protein of the original Wuhan-hu-1 virus.[9] Some emerging variants, which appear to be more transmissible or deadlier than the wild-type SARS-CoV-2, contain mutations in the spike protein, spurring vaccine efficacy concerns.[9] Trials of the Novavax, Janssen, and AstraZeneca vaccines in South Africa, where the B.1.351 variant of concern represents virtually all of the circulating SARS-CoV-2, seemed to justify those concerns.[9] Those trials found lower vaccine efficacy compared with trials in other countries where B.1.351 was not dominant.[9]

The pivotal trials of the Pfizer and Moderna vaccines were conducted mainly in the US before any cases of infection by B.1.351 or other variants of concern had been detected.[9] Most of the current data on the mRNA vaccines' efficacy against SARS-CoV-2 variants has come from laboratory studies in which researchers exposed serum samples from immunized individuals to genetically engineered versions of concerning variants and then measured neutralizing antibody titers.[9] These studies repeatedly have shown the vaccines elicit lower levels of neutralizing antibodies against SARS-CoV-2 variants than against older, more common isolates.[9] However, that still might be sufficient to protect against COVID-19, or at least severe COVID-19.[9] Although serum antibody levels correlate well with protection for many infectious diseases, protective levels have not yet been determined for SARS-CoV-2.[9] In addition to neutralizing antibodies, mRNA vaccines also induce virus-specific helper T cells and cytotoxic T cells that might help protect against infection.[9] Pfizer and Moderna have started evaluating the safety and immunogenicity of a third dose of the mRNA vaccine to see whether it would boost immunity to SARS-CoV-2 variants. Janssen is currently evaluating the efficacy of 2 doses, separated by 57 days, of its vaccine to improve outcomes in virus variants in a planned 30,000 patient study. Whether COVID-19 will join influenza as an infectious disease for which annual vaccination is required is not yet known.

Special Populations

The Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP), in collaboration with the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, have issued guidance indicating that Covid-19 vaccines should not be withheld from pregnant persons.[10-12] A recent article published in the New England Journal of Medicine summarized preliminary data obtained from several surveillance systems to address the safety of mRNA COVID-19 vaccines in pregnant women.[13] As of March 30, 2021, the vaccine-safety (v-safe) pregnancy registry call center attempted to contact 5230 persons who were vaccinated through February 28, 2021, and who identified during a v-safe survey as pregnant at or shortly after Covid-19 vaccination.[13] Among enrolled participants, most were 25 to 44 years of age (98.8%), non-Hispanic White (79.0%), and, at the time of interview, did not report a Covid-19 diagnosis during pregnancy (97.6%).[13] Receipt of a first dose of vaccine meeting registry-eligibility criteria was reported by 92 participants (2.3%) during the periconception period, by 1132 (28.6%) in the first trimester of pregnancy, by 1714 (43.3%) in the second trimester, and by 1019 (25.7%) in the third trimester.[13]

Among 827 participants who had a completed pregnancy, the pregnancy resulted in a live birth in 712 (86.1%), in a spontaneous abortion in 104 (12.6%), in stillbirth in 1 (0.1%), and in other outcomes (induced abortion and ectopic pregnancy) in 10 (1.2%).[13] A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation, and 700 of 712 pregnancies that resulted in a live birth (98.3%) were among persons who received their first eligible vaccine dose in the third trimester.[13] Adverse outcomes among 724 live-born infants — including 12 sets of multiple gestation — were preterm birth (60 of 636 among those vaccinated before 37 weeks [9.4%]), small size for gestational age (23 of 724 [3.2%]), and major congenital anomalies (16 of 724 [2.2%]); no neonatal deaths were reported at the time of interview.[13] Calculated proportions of pregnancy and neonatal outcomes appeared similar to incidences published in the peer-reviewed literature.[13]

Key Oregon Health Authority Talking Points

- The COVID-19 vaccines will not end the pandemic, but vaccination will. It is important that everyone is vaccinated to achieve community immunity.
- COVID-19 vaccines have been extensively evaluated in large-scale clinical trials. These trials involved adults from a diverse and inclusive range of races, ethnicities, and ages.
- COVID-19 vaccines are vetted for safety and efficacy by three independent scientific groups.

Racial and Ethnic Inequities in Oregon

The COVID-19 pandemic has affected everyone in Oregon, but it has not disproportionately affected certain communties.[14] In Oregon, the Latino community is experiencing the most pronounced inequities, compared to the white community:

- People who identify as white represent 75% of Oregonians. While they only comprise about half (48%) of COVID-19 cases, they account for 74% of vaccinations.[14]
- People who identify as Latino or Hispanic represent 13% of Oregonians. However, they comprise 26% of COVID-19 cases. Despite the disproportionate burden of COVID-19 cases in the Latino community, they account for only 5% of the vaccinations administered to date.[14]

Latino, Black, African Americans and Native American communities are also burdened by significant health inequities that enhance their risks from COVID-19. These health inequities are the product of systemic racism, toxic stress and other factors.[14] Future outreach and education efforts need to provide clear, accurate messages about how to prevent COVID-19 in Spanish and for audiences with low literacy.[15] These messages should be delivered by trusted messengers in community settings using appropriate media channels (e.g., Spanish television and radio).[15] The OHA has also developed resources in Spanish at the Vacnunacovid page.

Addressing Vaccine Hesitancy

"COVID-19 vaccines were developed too fast to be safe."

- The technology used to develop the new COVID-19 vaccines has been used to develop other vaccines and is not new.
- All COVID-19 vaccines have gone through rigorous studies to ensure they are as safe as possible. The Center for Disease control is continuing to watch for safety issues that are reported across the entire country.

"There were not enough participants in the clinical trials to declare the vaccines safe."

- All 3 COVID-19 vaccines enrolled tens of thousands of participants, many of whom were followed for 2 months after receiving the final dose, as is common with other vaccines.

Conclusions

Although 3 vaccines are currently authorized for use in the US, the emergence of virus variants is concerning. It is important to maximize availability of COVID-19 vaccines to all Oregonians to reduce transmission of the SARS-CoV-2 virus and prevent additional viral mutations. All available vaccines have proven efficacy and safety from large randomized controlled trials. Educating the public is vital to overcoming concerns about receiving the vaccine.

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Deprescribing Techniques to Minimize Safety Issues Associated with Inappropriate Polypharmacy

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It is common for Americans to take more than one medication. Up to 44% of men and 57% of women over the age of 65 years take over 5 medications per week.[1] Taking multiple medications is termed polypharmacy and is most commonly defined as 5 or more medications prescribed for regular use.[2, 3] Inappropriate polypharmacy can contribute to adverse drug reactions, hospitalizations, drug-drug interactions, poor adherence, lack of efficacy, geriatric syndromes, increased healthcare costs and decreased quality of life.[2] Antipsychotic polypharmacy in Medicaid programs has also been associated with higher drug expenditures.[4] A comprehensive medication review can help to identify patients who are candidates for medication discontinuation. This newsletter will focus on identifying patients at risk of inappropriate polypharmacy and discuss deprescribing techniques when appropriate.

Desprescribing: Benefits and Risks

Deprescribing is the planned and supervised process of dose reduction or stopping medications that may be causing harm or no longer providing benefit.[2, 5] Benefits of deprescribing may include a reduction in medication burden and harms, improved functioning and a decrease in health care costs.[2, 5, 6] Risks of deprescribing may include withdrawal symptoms, disease progression, reversal of drug interactions, or return of symptoms. Although there is limited high quality and consistent data evaluating deprescribing on clinical outcomes, evidence suggests that deprescribing is safe, practical, and beneficial in reducing inappropriate polypharmacy.[5, 7] Organizations including the National Institute for Health and Care Excellence (NICE) and World Health Organization recognize the importance of identifying inappropriate polypharmacy to decrease avoidable medication-related harms.[8, 9]

Target Populations

Patients who are most likely to benefit from deprescribing are described in **Table 1**. Older patients with polypharmacy are at higher risk of adverse drug reactions, drug interactions, nonadherence, falls and functional decline.[10, 11] It is important consider the patient's life expectancy, current level of functioning, and goals of care when evaluating certain preventive therapies that require significant time for benefit.[6, 12]

Prevalence of antipsychotic polypharmacy in adults is somewhere between 20% and 50%, despite limited evidence of increased efficacy with dual antipsychotic therapy.[3, 13, 14] Deprescribing may be beneficial in this population due to increased risk for drug-drug interactions and long-term harms.[13, 14] Adverse effects resulting from antipsychotic polypharmacy can include Parkinsonian side effects, extrapyramidal symptoms, sexual dysfunction, sedation, cognitive impairment, and metabolic syndromes.[14] Polypharmacy with psychiatric medications has been shown to be as high as 30-65% in children in foster care.[15-17]

Table 1. Candidates for Deprescribing[10, 11,18,13]

Patients with the following:
• Multiple progressive chronic diseases
• On medications without benefit
• Taking over 8 medications
• Having difficulty adhering to drug regimen
Older Patients who have one or more the following:
• Experiencing adverse drug reactions
• On high risk medications
• Severe frailty or cognitive decline
• At a high risk of falls and functional decline
• With an advanced or progressive disease

Target Medications

To determine drugs for deprescribing, a patient's medication list should be reviewed for valid indications, risk of harm, and perceived benefit.[5] All high-risk medications should be evaluated to determine if the risk of side effects outweigh the benefits. High risk medications include benzodiazepines, anticholinergics, digoxin, hypoglycemic agents, anticoagulants and opioids.[19] Lastly, tools such as the BEERS list and STOPP criteria can be used to identify medications for potential deprescribing in older patients (**Table 4**).[2] One way to identify potentially inappropriate medications is to perform a comprehensive medication review, asking questions such as those in **Table 2**.

Table 2: Questions to Evaluate for Potential Deprescribing During a Comprehensive Medication Review [5]

- Is there a valid indication?
- Is the patient actually taking the drug?
- Is there significant toxicity or an obvious contraindication to this medication?
- Do the harms outweigh the benefits?
- Does the treatment fit with the patient's goals of care?
- Are disease symptoms stable or absent?
- Are withdrawal symptoms or disease recurrent unlikely, or safely manageable?

Deprescribing Safely

Using a patient-centered approach, patients should be engaged and involved in the deprescribing decision-making process. Discuss goals of care to assess which preventive drugs fit with patient preferences and life expectancy.[6] Drugs can be prioritized for discontinuation based on their potential harms, risk of withdrawal symptoms and patient desire to stop therapy.

A plan to monitor for withdrawal effects and tolerability of deprescribing is essential to ensure successful and safe deprescribing.[6] Prior to deprescribing a medication, providers should identify if a medication taper is needed, the risk of condition resurgence, and how to prevent patient discomfort.[19] A clear plan for the patient to re-initiate or taper up if needed should be established.[19] **Table 3** includes medications with withdrawal effects and strategies to minimize symptoms.

Table 3. Recommendations for Deprescribing in select Medication Classes[7, 20-24]

Drug Class	Withdrawal Symptoms	Prevention Strategies
Acetylcholinest-erase Inhibitors	Agitation, hallucinations	Decrease dose by 50% every 4 weeks.
Anticonvulsants	Anxiety, depression, seizures	Decrease dose and discontinue after 4 weeks or longer.
Antidepressants	Akathisia, anxiety, headache, Insomnia, irritability	Decrease dose by 25% every 4 weeks.
Antiparkinsonian	Hypotension, psychosis, tremor	Decrease dose by 25% every 4 weeks.
Antipsychotics	Dyskinesias, insomnia, nausea	Decrease dose by 25-50% every 1-2 weeks.
Benzodiazepines	Agitation, anxiety, confusion, insomnia, seizures	Decrease dose very slowly, by no more than 25% every 2 weeks. Monitor every 1 week during taper.
Beta Blockers	Angina, anxiety, hypertension, tachycardia, MI	Decrease dose by 25-50% every 4 weeks. Monitor blood pressure and heart rate after each dose change.
Opioids	GI cramping, anxiety, chills, diarrhea, insomnia	Decrease dose by 5-25% every 1-4 weeks, depending on patient tolerability.
Proton Pump Inhibitors	GI upset, heartburn	Decrease dose by 50% initially. Monitor at 4 and 12 weeks. H2RAs may be considered as add-on to manage symptoms.

Abbreviations: GI-gastrointestinal; H2RAs: Histamine-2 Receptor Antagonists; MI-myocardial infarction.

Deprescribing Tools

Listed in **Table 4** are some references available to help evaluate polypharmacy and safely deprescribe medications. Additionally, evidence-based deprescribing guidelines are available for the following drug classes: proton pump inhibitors, antipsychotics for dementia, benzodiazepines, antihyperglycemics, and acetylcholinesterase inhibitors.[23, 25-27] Describing guidelines and algorithms for these medication classes, as well as a mobile-based app, are available on deprecribing.org. An example is presented in **Appendix 1**.[26]

Table 4. Tools to Assist with Deprescribing

Tool Name	Description
Drug Burden Index[28]	Assess anticholinergic and sedative burden.
Deprescribing.org Evidence-based deprescribing guidelines[20]	Resources for patients, healthcare providers, and researchers on how to safely deprescribe PPIs, BDZ, antihyperglycemic agents, antipsychotics, acetylcholinesterase inhibitors.
Beer's Criteria[29]	Helps identify potentially inappropriate medications in the elderly.
STOPP/START[12]	Helps facilitate medication reviews in the elderly with multiple comorbid conditions.
NSW Deprescribing Tools[30]	Guidelines for psychotropic, neurological, genitourinary, allergy and anaphylaxis, analgesics, GI drugs, and information leaflets.
US deprescribing Research Network[31]	Deprescribing guidelines, algorithms, educational videos for clinicians, and guidance for performing medication reviews.

Abbreviations: BDZ – benzodiazepines; GI – gastrointestinal; NSW – New South Wales; PPI – proton pump inhibitor

Conclusion

A patient-centered deprescribing practice is a reasonable solution to address polypharmacy. A full medication review should be performed, specifically targeting the elderly, young children, patients with multiple prescribers, and patients with trouble managing their current medication regimen. Medications to target include those at high risk for potential or actual harms, and drugs without evidence of benefit in the individual patient. Safe deprescribing requires thorough patient education and close follow-up to monitor for adverse withdrawal effects and disease resurgence. Resources and tools for prescribers help facilitate patient discussions about polypharmacy and safe deprescribing.

Peer Reviewed By: Andrew Gibler, PharmD, Director of Pharmacy, Legacy Mt Hood Med Center, Unity Center for Behavioral Health, and Legacy Emanuel Apothecary.

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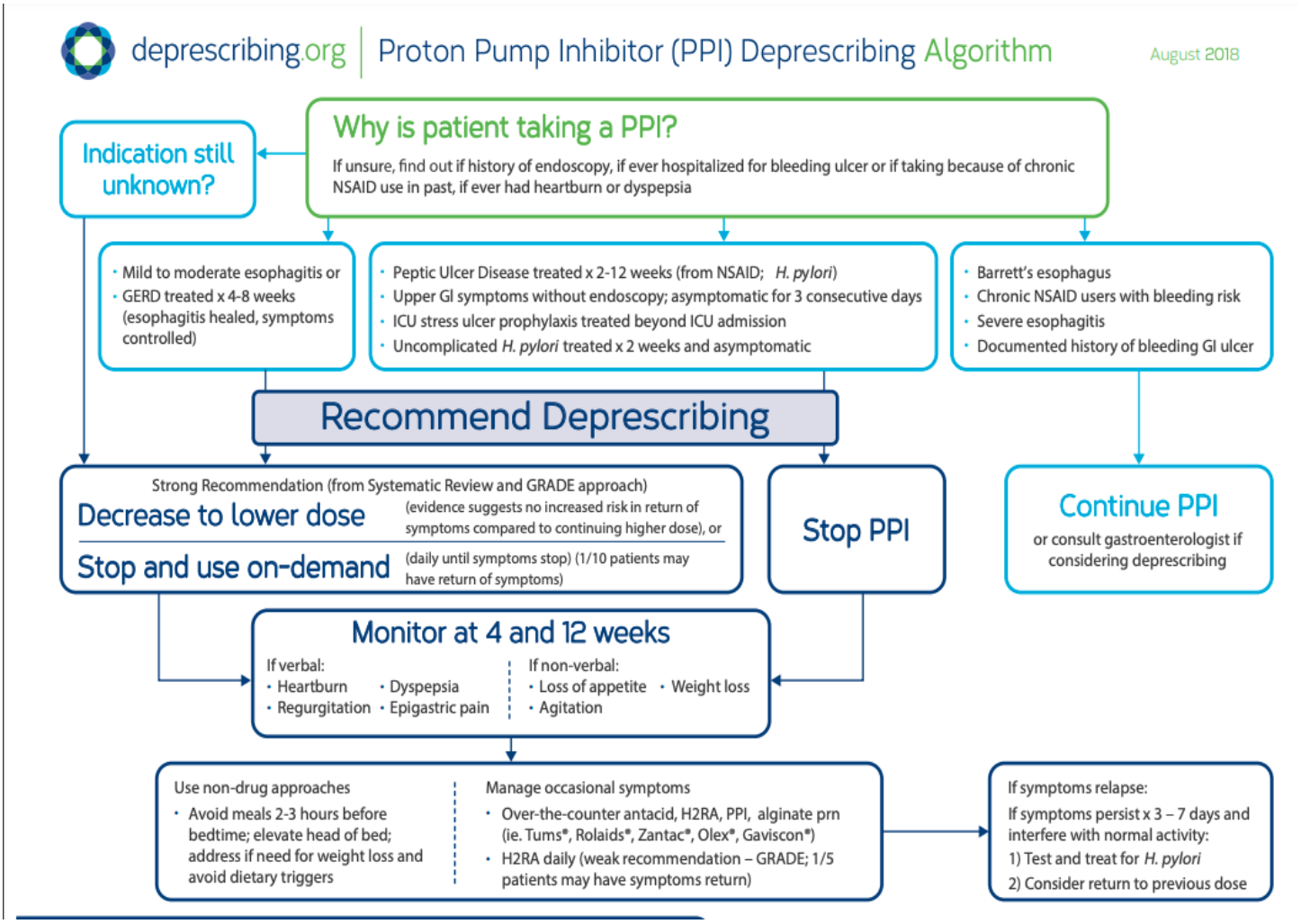
31. US deprescribing research Network. Resources for Clincians. 2021. (Accessed April 4, 2021). https://deprescribingresearch.org/.

Appendix 1: Algorithm for Desprescribing Proton Pump Inhibitors:[26]



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Prior Authorization Update: Evinacumab

Purpose of this update:
The purpose of this update is to develop criteria for ongoing therapy with evinacumab. Evidence for evinacumab was previously reviewed by the Pharmacy and Therapeutics Committee in August 2021.[1]

Recommendation
- Update prior authorization to include renewal criteria.

References
1. Herink, M. Drug Use Research and Management Program. Drug Class Update with New Drug Evaluation: Other Dyslipidemia Drugs. August 2021. https://www.orpdl.org/durm/meetings/meetingdocs/2021_08_05/archives/2021_08_05_OtherDyslipidemia_ClassUpdate.pdf. Accessed September 7, 2021.

Appendix 1. Proposed Prior Authorization Criteria

Evinacumab

Goal(s):
- Promote use of evinacumab that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:
- 6-12 months

Requires PA:
- Evinacumab (Evkeeza™)

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; go to #2	
2. Is the patient 12 years or older with a diagnosis of homozygous or familial hypercholesterolemia (HoFH) diagnosed by genetic testing or the following clinical criteria? • Untreated LDL-C > 500 mg/dl or treated LDL-C > 300 mg/dl	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Does the patient still have an LDL-C of ≥ 100 mg/dl while taking a maximally tolerated dose (or have a contraindication) of all the following agents: • Statin, and • Ezetimibe, and • PCSK9 inhibitor (alirocumab or evolocumab)	**Yes:** Go to #4 Recent LDL-C _____ mg/dL Date: _____	**No:** Pass to RPh; deny for medical appropriateness.
4. Is the patient of childbearing potential?	**Yes:** Go to #5	**No:** Approve for up to 12 months
5. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #6
6. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Did the patient achieve a LDL-C reduction to less than 70 mg/dl OR a 30% decrease from baseline prior to adding evinacumab?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness

Renewal Criteria		
3. Is the patient adherent with other lipid-lowering therapies, including maximally tolerated statin, ezetimibe, and PCSK9 inhibitor therapy?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence	**No:** Pass to RPh; deny for medical appropriateness

P&T / DUR Review: *10/21 (MH); 08/21 (MH)*
Implementation: *9/1/21*

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Prior Authorization Criteria Update: Esketamine

Purpose of Update:

The purpose of this update is to clarify recommended dose of esketamine beyond 4 weeks and use of esketamine in patients with substance use disorder.

Evidence for use of esketamine in treatment-resistant depression[1] and for acute treatment in patients with depression and suicidal ideation[2] has been previously evaluated by the Pharmacy and Therapeutics Committee. For these populations, esketamine may improve depression symptoms compared to placebo with an average improvement of 4 points on the Montgomery-Asberg Depression Rating Scale (MADRS) compared to placebo,[1,2] but does not improve suicidal ideation (based on low quality evidence).[2] A 2 point improvement on MADRS may be associated with a clinically significant improvement.[3]

Esketamine has a box warning for misuse and abuse,[4] and current safety criteria limit use in patients with a history of substance use disorder. In clinical trials, common adverse effects associated with esketamine treatment include sedation (in 48-61% of treated patients), disassociation (in 61-84% of patients), increases of more than 40 mmHg diastolic or 25 mmHg systolic blood pressure (in 8-19% of patients), and cognitive impairment (incidence not reported).[4] It is unknown how illicit drug use may influence or impact frequency or severity of adverse events with esketamine, though drugs with similar adverse event profiles may increase risk of adverse effects when used concomitantly. Because there is a wide variety of types and severities of substance use disorder, the proposed edits remove this question from the criteria in order to accommodate patients with a remote history of substance use disorder when benefits of treatment may outweigh risks. Clarifications to maintenance dose of esketamine are also suggested in the renewal criteria. Esketamine 56 or 84 mg twice weekly has been studied for acute use (up to 4 weeks) in patients with suicidal ideation, but use of twice weekly dosing beyond 4 weeks has not been evaluated.[4] The FDA-approved maintenance dose in patients with treatment-resistant depression is 56 or 84 mg every 1 to 2 weeks.[4]

Recommendation:

- Update the safety edit for esketamine to clarify appropriate maintenance dose and use in patients with a history of substance use disorder.

References:

1. Sentena, K. Drug Use Research and Management Program. Drug Class Update with New Drug Evaluation: Antidepressants. July 2019. https://www.orpdl.org/durm/meetings/meetingdocs/2019_07_25/archives/2019_07_25_Antidepressant_ClassUpdate.pdf. Accessed September 7, 2021.
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Appendix 1. Proposed Safety Edits

Esketamine (Spravato)

Goal(s):
To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:
Up to 6 months

Requires PA:
Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
~~Does the patient have a history of substance abuse?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness.~~	~~**No:** Go to #7~~
6. Does the patient have treatment resistant depression (failure of two separate antidepressant~~s~~ trials which were each given for at least 6~~-8~~ weeks at ~~FDA approved~~target doses)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
7. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
8. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4

Renewal Criteria		
2. Is the request for administration of esketamine once weekly?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness. Esketamine is administered once weekly after 4 weeks. Other dosing frequencies have not been adequately studied.
~~2.~~3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)~~(84 mg twice weekly for a maximum of 28 days)~~

P&T/DUR Review: 10/21 (SS); 2/21(SS); 7/19 (KS)
Implementation: 3/1/21; 8/19/19

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Drug Use Evaluation: Pre-exposure Prophylaxis for HIV

Research Questions:

1. What proportion of fee-for-service (FFS) patients at high risk of HIV transmission receive pre-exposure prophylaxis (PrEP)?

Conclusions:

- In an evaluation of patients currently enrolled in FFS Medicaid on October 1, 2021, a total of 989 patients were identified who had recent HIV testing or risk factors for HIV transmission in the previous 6 months. The majority of patients (77%) were identified based on a single HIV test. Routine HIV testing is recommended at least once for all adults and more frequently (every 3 to 12 months) in patients with risk factors for transmission.[1,2]
- The following diagnoses were identified in the previous 6 months which may indicate high risk for HIV transmission: 20% of patients (n=193) had a diagnosis from medical claims indicating a sexually transmitted infection (STI), 5% of patients (n=50) had a diagnosis of high-risk sexual behavior, and 10% of patients (n=97) had a diagnosis indicating potential viral exposure.
- Very few of these patients (<1%, n=8) had FFS pharmacy claims for PrEP.

Recommendations:

- Develop an educational retrospective drug use review (DUR) program to improve provider knowledge of PrEP for patients with a recent STI, diagnosis of high-risk sexual behavior, or potential viral exposure.

Background

Prophylaxis for HIV is recommended as preventative therapy in patients with recent potential exposure to HIV (post-exposure prophylaxis [PEP]) and in patients at high risk for HIV transmission (pre-exposure prophylaxis [PrEP]). Transmission of HIV primarily occurs through high-risk sexual behavior or exposure to infected blood. Risk of HIV transmission is primarily dependent on risk associated with a specific behavior and likelihood that a sex partner or drug injection partner is living with HIV.[3] For example, HIV transmission is higher with receptive anal intercourse compared to insertive anal intercourse or penile-vaginal intercourse.[3] Similarly, injection drug use associated with needle-sharing has a high risk of HIV transmission. Risk factors which increase the chance of HIV transmission include being in a relationship with a partner living with HIV, inconsistent use of condoms during anal sex or with persons with risk factors for HIV transmission, or a diagnosis of a sexually transmitted infection within the past 6 months.[3]

The US Preventative Services Task Force (USPSTF) currently recommends that therapy with PrEP be considered for the following populations:[3]

1. Persons who inject drugs who have shared use of drug injection equipment
2. Men who have sex with men who are sexually active and have at least one of the risk factors described above
3. Heterosexual and sexually active persons with at least one of the risk factors described above

Recommendations for frequency of HIV testing vary slightly between organizations. The Centers for Disease Control recommends screening at least once in all adults and adolescents (13 to 64 years of age), with at least yearly testing in individuals with high risk of transmission.[1] The USPSTF recommends routine screening for HIV in all patients 15-65 years of age especially in areas with high community prevalence.[2] More frequent testing (every 3 to 6 months) is recommended for individuals at high risk for HIV transmission.[2] In patients being considered for PrEP, HIV testing should be done prior to therapy initiation to rule out an active infection and every 3 months during PrEP treatment.[3]

Methods:

This analysis evaluated a "snapshot" in time for Medicaid patients with risk factors for HIV transmission. Data was evaluated for members enrolled in Medicaid as of October 1, 2021. Adult or adolescent FFS patients (≥10 years of age) were included if they were currently enrolled had either routine HIV testing during the past 6 months (see codes in **Appendix 1**) or had claims indicating potential risk for HIV transmission. Potential risk for HIV transmission was defined based on medical claims within the past 6 months and included the following groups:

- patients with at least 2 claims for HIV testing at least 30 days apart OR
- patients with an STI diagnosis (ICD10 codes: A50x-A64x, O981-O9833, R8581, R8582, R8781x, R8782x) OR
- patients with other high-risk sexual behavior (ICD10 codes: Z725x) OR
- patients with potential viral exposure (ICD10 codes: Z202, Z206, Z7721, Z205)

Details for descriptions of ICD-10 codes are available in **Appendix 1**. Because ICD-10 diagnosis codes categorize substance use disorders based on substance type rather than route of administration, injection drug use was not captured in this analysis as a risk factor for HIV transmission.

The drug combinations currently FDA approved for PrEP include combination emtricitabine/tenofovir disoproxil fumarate and emtricitabine/tenofovir alafenamide. Paid FFS pharmacy claims for PrEP were identified in the previous 120 days based on drug codes (HSNs 026515 and 043241). Patients were excluded if they had any pharmacy claims for active HIV drug treatment (excluding PrEP HSNs) within that time. Patients were excluded if they had Medicare coverage, limited Medicaid drug benefits (benefit plans CWM, MND, BMM, BMD, MED), had other insurance (TPL), or were enrolled in a CCO during the prior 6 months as pharmacy claims data may be inaccurate or incomplete for these populations.

Results:

Overall, 989 patients were included in the analysis. Most patients were over 18 years of age and identified as female upon enrollment with Medicaid. However, historically data has been collected patients based on sex assigned at birth rather than gender and does not regularly include non-binary gender options. The majority of patients (77%) were identified based on a single HIV test in the past 6 months (**Table 1**). HIV testing itself is not a definitive indication for PrEP, and current guidelines recommend routine testing for all adults and adolescents. However, a significant proportion of patients had other diagnoses which may indicate high risk for HIV transmission. For example, 20% (n=193) of patients had a diagnosis from medical claims indicating a sexually transmitted infection in the previous 6 months, 5% (n=50) of patients had a diagnosis of high-risk sexual behavior, and 10% (n=97) of patients had a diagnosis indicating potential viral exposure. Diagnoses are not mutually exclusive, and patients with multiple diagnoses may be included in more than one category. However, only a small proportion of patients (~10%) were included in the analysis based on more than one diagnosis. Very few patients had multiple subsequent HIV tests. Multiple HIV tests over a short timeframe may indicate frequent testing in a patient at high risk for transmission or a provider performing repeated tests due to suspicion of an active HIV infection. Only 8 patients (<1%) were identified who had claims for PrEP in the previous 120 days (**Table 2**).

Of note, very few white patients were identified, and more than half of patients with HIV testing or risk factors for HIV transmission were American Indian or Alaskan Natives (53%). About 24% of patients included in this analysis identified as other non-white racial groups. This group includes, but not limited to, patients identifying as Black, Hispanic, Asian, and Pacific Islander.

Table 1. Patients with recent HIV testing or potential risk factors for HIV transmission AND without claims for PrEP

		Patients	%
	N=	**981**	
Patients with HIV testing		754	76.9%
Risk factor category (patients may be counted more than once)			
Patients with ≥ 2 HIV tests at least 30 days apart		11	1.1%
STI diagnosis in the past 6 months		193	19.7%
Patients with other high risk sexual behavior in the past 6 months		50	5.1%
Potential viral exposure in the past 6 months		97	9.9%
Number of diagnoses used to identify patients for inclusion (grouped by any HIV testing, STI, or other high-risk diagnoses)			
1		876	89.3%
2		97	9.9%
3		8	0.8%
Demographics			
Race			
White		17	1.7%
American Indian/Alaskan Native		525	53.5%
Unknown		204	20.8%
Other		235	24.0%
Female		812	82.8%
Average Age in years (min-max)		32	(12-63)
10-18		46	4.7%
19-64		935	95.3%
>=65*		0	0.0%

* Patients enrolled in Medicare were excluded from this analysis as Medicaid is not the primary payer in this population and claims data is likely incomplete

Table 2. Patients with recent HIV testing or potential risk factors for HIV transmission

	Patients	%
Current FFS patients with HIV testing or risk factors for HIV transmission	989	
Patients with PrEP claims in the past 120 days	8	0.8%
Patients without PrEP claims in the past 120 days	981	99.2%

Discussion and Limitations:

- This analysis evaluates a single point in time and captures only a snapshot of patients who were enrolled in Medicaid during October 2021. Populations and enrollment may change over time.
- This analysis likely does not capture all patients who may be at risk for HIV transmission. Patients with potential risk for HIV transmission were identified based on diagnoses on medical claims. In particular, patients with injection drug use were not captured in this analysis as ICD-10 diagnosis codes do not differentiate between routes of administration for patients with substance use disorder. Additionally, because there is often a delay in billing for medical claims, diagnoses which were included in the analysis are likely incomplete.
- Billed diagnoses may not accurately reflect actual diagnoses in the patient's chart. For example, providers may submit medical claims with diagnoses of STI or HIV when they are just performing screening tests for these infections.
- Because this analysis only evaluates claims data, many of the clinical considerations and risk-benefit evaluation surrounding use for PrEP are not captured. For example, it is unclear whether providers are already discussing use of PrEP or other risk mitigation strategies (such as routine condom use) with their patients. Similarly, it is unknown how many patients may have already been offered use of PrEP and declined based on their individual situation.
- The specific ICD-10 codes used in this analysis to identify HIV testing and at-risk groups may influence demographics for included patients. For example, 83% of patients identified as female, and there are multiple ICD-10 codes associated with STIs during pregnancy which may inadvertently result in inclusion of more female patients. Similarly, HIV testing is frequently performed as part of routine screening during a pregnancy, which may have resulted in inclusion of more female patients in this analysis.
- A large proportion of American Indian/Alaskan Native patients were identified in this analysis. This data is likely influenced in part by method of enrollment with Medicaid for American Indian/Alaskan Native patients. Unlike most other patient groups, American Indian/Alaskan Native patients are not automatically assigned to a Coordinated Care Organization upon enrollment with Medicaid, resulting in a larger proportion of these patients in FFS Medicaid.
- It is unclear why so few white patients were included in this analysis. HIV testing is recommended at least once in all adults, and FFS Medicaid typically includes a large proportion of patients who identify as white. Multiple factors may contribute to this discrepancy. For example, the diagnoses included in this analysis are often stigmatized which could result in variability in access to testing or billing for diagnoses depending on the patient, provider, or setting. Additionally, multiple programs within the state offer free HIV and STI testing which may be utilized more by some groups than others.

References:

1. Center for Disease Control and Prevention. HIV Testing. Updated June 9, 2020. Accessed Novermber 1, 2021. https://www.cdc.gov/hiv/testing/index.html
2. Owens DK, Davidson KW, Krist AH, et al. Screening for HIV Infection: US Preventive Services Task Force Recommendation Statement. *Jama.* 2019;321(23):2326-2336.
3. Owens DK, Davidson KW, Krist AH, et al. Preexposure Prophylaxis for the Prevention of HIV Infection: US Preventive Services Task Force Recommendation Statement. *Jama.* 2019;321(22):2203-2213.

Appendix 1: Drug coding
Table A1. PrEP Drug regimens

HSN	Route	Generic
043241	PO	emtricitabine/tenofov alafenam
026515	PO	emtricitabine/tenofovir (TDF)

Table A2. Diagnosis codes descriptions used to identify high risk for HIV transmission

ICD-10 code	Generic description	Category
A50	Congenital syphilis	STI
A51	Early syphilis	STI
A52	Late syphilis	STI
A53	Other and unspecified syphilis	STI
A54	Gonococcal infection	STI
A55	Chlamydial lymphogranuloma (venereum)	STI
A56	Other sexually transmitted chlamydial diseases	STI
A57	Chancroid	STI
A58	Granuloma inguinale	STI
A59	Trichomoniasis	STI
A60	Anogenital herpesviral [herpes simplex] infections	STI
A63	Oth predominantly sexually transmitted diseases, NEC	STI
A64	Unspecified sexually transmitted disease	STI
O981	Syphilis compl preg/chldbrth	STI
O9811	Syphilis complicating pregnancy	STI
O98111	Syphilis complicating pregnancy, first trimester	STI

O98112	Syphilis complicating pregnancy, second trimester	STI
O98113	Syphilis complicating pregnancy, third trimester	STI
O98119	Syphilis complicating pregnancy, unspecified trimester	STI
O9812	Syphilis complicating childbirth	STI
O9813	Syphilis complicating the puerperium	STI
O982	Gonorrhea compl preg/chldbrth	STI
O9821	Gonorrhea complicating pregnancy	STI
O98211	Gonorrhea complicating pregnancy, first trimester	STI
O98212	Gonorrhea complicating pregnancy, second trimester	STI
O98213	Gonorrhea complicating pregnancy, third trimester	STI
O98219	Gonorrhea complicating pregnancy, unspecified trimester	STI
O9822	Gonorrhea complicating childbirth	STI
O9823	Gonorrhea complicating the puerperium	STI
O983	Oth infections w sexl mode of transmiss compl preg/chldbrth	STI
O9831	Oth infections w sexl mode of transmiss comp pregnancy	STI
O98311	Oth infect w sexl mode of transmiss comp preg, first tri	STI
O98312	Oth infect w sexl mode of transmiss comp preg, second tri	STI
O98313	Oth infect w sexl mode of transmiss comp preg, third tri	STI
O98319	Oth infect w sexl mode of transmiss comp preg, unsp tri	STI
O9832	Oth infections w sexl mode of transmiss comp childbirth	STI
O9833	Oth infections w sexl mode of transmiss comp the puerperium	STI
R8581	Anal high risk human papillomavirus (HPV) DNA test positive	STI
R8582	Anal low risk human papillomavirus (HPV) DNA test positive	STI
R8781	High risk HPV DNA test positive from female genital organs	STI
R87810	Cervical high risk HPV DNA test positive	STI
R87811	Vaginal high risk HPV DNA test positive	STI
R8782	Low risk HPV DNA test positive from female genital organs	STI
R87820	Cervical low risk HPV DNA test positive	STI
R87821	Vaginal low risk HPV DNA test positive	STI
Z725	High risk sexual behavior	High risk sexual behavior
Z7251	High risk heterosexual behavior	High risk sexual behavior
Z7252	High risk homosexual behavior	High risk sexual behavior
Z7253	High risk bisexual behavior	High risk sexual behavior
Z202	Contact w and exposure to infect w a sexl mode of transmiss	Potential viral exposure

Z205	Contact with and (suspected) exposure to viral hepatitis	Potential viral exposure
Z206	Contact w and (suspected) exposure to human immunodef virus	Potential viral exposure
Z7721	Contact w and exposure to potentially hazardous body fluids	Potential viral exposure

Table A3. Codes for HIV testing

Procedure Code	Description
G0432	Infectious Agent Antibody Detection By Enzyme Immunoassay (Eia) Technique, Hiv-1 And/Or Hiv-2, Scree
G0433	Infectious Agent Antibody Detection By Enzyme-Linked Immunosorbent Assay (Elisa) Technique, Hiv-1 An
87901	Analysis Test By Nucleic Acid For Hiv-1 Virus
87906	Analysis Test By Nucleic Acid For Hiv-1 Virus, Other Region
86314	Hiv (Htlv-Iii) Antibody Detection; Confi
86312	Hiv (Htlv-Iii) Antibody Detection; Immun
G0298	Hiv Antigen/Antibody, Combination Assay, Screening
G0475	Hiv Antigen/Antibody, Combination Assay, Screening
0575F	Hiv Rna Control Plan Of Care, Documented (Hiv)
3502F	Hiv Rna Viral Load Below Limits Of Quantification (Hiv)
3503F	Hiv Rna Viral Load Not Below Limits Of Quantification (Hiv)
87806	Detection Test By Immunoassay For Hiv-1
86311	Hiv, Antigen
87390	Detection Test By Immunoassay Technique For Hiv-1
87389	Detection Test By Immunoassay Technique For Hiv-1 And Hiv-2
S3645	Hiv-1 Antibody Testing Of Oral Mucosal Transudate
87534	Detection Test By Nucleic Acid For Hiv-1 Virus, Direct Probe Technique
87535	Detection Test By Nucleic Acid For Hiv-1 Virus, Amplified Probe Technique
87536	Detection Test By Nucleic Acid For Hiv-1 Virus, Quantification
G0100	Hiv-1, Viral Load, Quanitative
86703	Analysis For Antibody To Hiv-1 And Hiv-2 Virus
86701	Analysis For Antibody To Hiv -1 Virus
87391	Detection Test By Immunoassay Technique For Hiv-2
86702	Analysis For Antibody To Hiv-2 Virus
87537	Detection Test By Nucleic Acid For Hiv-2 Virus, Direct Probe Technique
87538	Detection Test By Nucleic Acid For Hiv-2 Virus, Amplified Probe Technique
87539	Detection Test By Nucleic Acid For Hiv-2 Virus, Quantification
86689	Confirmation Test For Antibody To Human T-Cell Lymphotropic Virus (Htlv) Or Hiv

86687	Analysis For Antibody To Human T-Cell Lymphotropic Virus, Type 1 (Htlv-1)
86688	Analysis For Antibody To Human T-Cell Lymphotropic Virus, Type 2 (Htlv-2)
PUB02	Omap: Public Health Hiv Screening & Confirmation Testing
G0435	Infectious Agent Antibody Detection By Rapid Antibody Test, Hiv-1 And/Or Hiv-2, Screening
87904	Analysis Test By Nucleic Acid For Hiv-1 Virus, Each Additional Drug Tested
87903	Analysis Test By Nucleic Acid For Hiv-1 Virus, First Through 10 Drugs Tested

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Drug Class Update with New Drug Evaluation: Glucagon

Date of Review: December 2021

Date of Last Review: February 2020
Dates of Literature Search: 12/01/2019 - 08/06/2021

Generic Name: dasiglucagon

Brand Name (Manufacturer): Zegalogue (Zealand Pharma)
Dossier Received: no

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

Purpose for Class Update: The purpose of the glucagon class update is to evaluate new literature published since the last review and to evaluate the efficacy and safety of dasiglucagon, a new glucagon formulation.

Research Questions:
1. What is the new comparative evidence for efficacy of the different glucagon formulations (i.e., intranasal, subcutaneous [SC], intramuscular [IM], intravenous [IV]) used for the treatment of severe hypoglycemia for the outcomes of time to glucose normalization and resolution of hypoglycemia symptoms?
2. What is the comparative evidence for safety between the different glucagon formulations?
3. Are there subpopulations based on specific demographic characteristics in which certain glucagon formulations would be more effective or cause less harm in the treatment of hypoglycemia?

Conclusions:
- There was no new, high quality, comparative evidence identified for the different glucagon formulations.
- Three trials informed the approval of dasiglucagon: 2 trials in adults and one trial in children and adolescents. The overwhelming majority of study participants in the dasiglucagon trials were white (range, 92% to 100%) and the drug was studied in a tightly controlled inpatient setting. These factors reduce the applicability to the Oregon Medicaid population. There is moderate quality evidence that dasiglucagon improves time to plasma glucose recovery relative to placebo.
    - In adult patients, time to glucose recovery was 10 minutes compared to 35-40 minutes for placebo (P<0.001 for both studies; no confidence intervals [CI] provided).[1,2]
    - In children and adolescents (ages 6-17 years) time to glucose recovery was 10 minutes for dasiglucagon and 35 minutes for placebo (P<0.001; no CI provided).[3]

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- Two trials used glucagon as an active control (no formal statistical comparisons). Results of glucose recovery within 30 minutes suggest similar efficacy between dasiglucagon and glucagon.[2,3]

- Adverse events that occurred more often with dasiglucagon compared to placebo were nausea, vomiting, headache and injection site pain. No serious adverse events were reported.[4]
- New contraindications were added to labeling for generic glucagon, GlucaGen®, Gvoke®, and Baqsimi® products in patients with pheochromocytoma, glucagonoma or insulinoma (**Table 2**).
- There was insufficient evidence to determine if certain glucagon formulations would be more effective or associated with less harm in certain subgroups based on any demographic characteristic.

Recommendations:
- Recommend dasiglucagon remain non-preferred with no changes to the preferred drug list (PDL).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- The glucagon class was last reviewed in February of 2020, at which time a new PDL class was created. Preferred product designation was assigned to one intranasal product and 2 SC products (that require reconstitution); Baqsimi®, GlucaGen®, and glucagon emergency kit, respectively.
- Products requiring prior authorization (PA) are subject to the general non-preferred PA criteria.

Background:
Hypoglycemia requiring treatment is most commonly experienced in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes (T2DM) who use antidiabetic therapies to normalize glucose levels.[5] The prevalence of severe hypoglycemia is thought to be as high as 3 episodes a year in patients with T1DM, but infrequent in patients with T2DM.[5] Hypoglycemia is associated with many symptoms, including tremor, palpitations, anxiety, sweating, hunger and, in rare cases, seizures and coma. Case reports suggest that an average of 7% of deaths in patients with T1DM are due to hypoglycemia.[6] Hypoglycemia symptoms can appear at glucose levels of 65 mg/dL or lower; however, some individuals are less sensitive to glucose changes and are asymptomatic at low blood glucose levels.[5]

Hypoglycemia can be defined as severe hypoglycemia (which requires assistance from another person to administer carbohydrate or glucagon), symptomatic hypoglycemia (symptoms with blood glucose less than 70 mg/dL), asymptomatic hypoglycemia (no symptoms but blood glucose less than 70 mg/dL), and pseudohypoglycemia (typical symptoms are present but glucose values are 70 mg/mL or greater).[5,6]

It is recommended to treat hypoglycemia by administering 15-20 grams of fast-acting carbohydrate, such as glucose tablets, hard candy, or sweetened fruit juice.[7,8] Fifteen grams of glucose is required to increase blood glucose levels approximately 37 mg/dL within 20 minutes.[9] Intravenous dextrose may also be administered by a medical professional in medical emergencies. Administration of glucagon is an option in patients with severe hypoglycemia who are not being treated in a medical setting.[5,7] Glucagon stimulates endogenous glucose production to increase blood glucose levels. Glucagon given SC or IM increases blood glucose 54 mg/dL to 216 mg/dL in 60 minutes.[9] Guidelines recommend patients with T1DM always carry a form of glucagon (subcutaneous, intramuscular or nasal) that can be administered by a caregiver if needed.[10]

Glucagon formulations available in the U.S. include glucagon kits that require reconstitution for injection (e.g., GlucaGen® Hypokit and Glucagon for Injection), ready-to-use SC glucagon injectable products (e.g., Gvoke®) and intranasal glucagon (e.g., Baqsimi®) **(Table 1)**. [11–14] Reconstituted glucagon products can be given SC, IM or IV but the ready-to-use formulations can be administered SC only. Nasal glucagon is administered intranasally via a device which dispenses a glucagon powder that is readily absorbed by the mucous membranes.[5] Administration of IV, IM or SC glucagon is usually associated with glucose recovery in about 15 minutes, while it is slightly longer (about 18 minutes) for intranasally administered glucagon.

Table 1. Approved Glucagon Products

Brand Name (Manufacturer)	Indication(s)	Reconstitution	Strength/Route	Dose and Frequency
Baqsimi®[12] (Lilly)	Treatment of severe hypoglycemia in patients with diabetes ages 4 years and older	No	3 mg intranasal spray powder	1 spray into 1 nostril Dose may repeat once after 15 minutes if no response
GlucaGen®[13] (Novo Nordisk)	Treatment of hypoglycemia; also used as a diagnostic aid	Yes	1 mg/ 1mL SC, IM, IV	Adults and children ≥ 55 lbs. (25 kg) 1 mL Children < 55 lbs. (25 kg): 0.5 mL If weight unknown: Children < 6 years: 0.5 mL Children 6 years and older: 1 mL (must be reconstituted) Dose may be repeated if no response*
Glucagon Emergency kit[11] (Lilly)	Treatment for severe hypoglycemia in patients with diabetes mellitus; also used as a diagnostic aid	Yes	1 mg/ 1 mL SC, IM, IV	Adults and children ≥44 lbs. (20 kg): 1 mg Children <44 lbs. (20 kg): 0.5 mg (or dose equivalent to 20-30 mcg/kg) (1 mg/mL reconstituted) Dose may be repeated if no response*
Gvoke®[14] (Xeris) Pre-filled syringe and auto-injector	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and older	No	0.5 mg/0.1 mL or 1 mg/0.2 mL SC	Adults and pediatric patients 12 years and older: 1 mg Pediatric patients 2 to under 12 years: < 45 kg: 0.5 mg ≥ 45 kg: 1 mg Dose may be repeated after 15 minutes if no response

Zegalogue®[4] (Zealand)	Treatment of severe hypoglycemia in adults and pediatric patients 6 years and older	No	0.6 mg/ 0.6 mL SC	Adults and pediatrics: 0.6 mg Dose may be repeated after 15 minutes if no response

Abbreviations: IM – intramuscular; IV -intravenous; SC – subcutaneous
Key: * Dosing interval not specified

Study endpoints frequently used to determine the efficacy of glucagon products are normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms.

There were 21 claims for glucagon products for Oregon Health Plan (OHP) fee-for-service (FFS) patients last quarter. Most prescription claims were for glucagon kits; however, intranasal glucagon and pre-filled syringes/auto-injectors were also prescribed. GlucaGen®, glucagon emergency kit, and Baqsimi® nasal spray are preferred. All claims were for preferred products. Non-preferred products are subject to the general non-preferred drug PA criteria.

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

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

Systematic Reviews:
None were identified.

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[15–17]

New Guidelines:
None identified

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Glucagon	Gvoke Hypopen	July 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with insulinoma because of the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis
Glucagon	NA	July 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure and in patients with glucagonoma when used as a diagnostic aid due to the risk of hypoglycemia
Glucagon	GlucaGen	March 2021	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with glucagonoma when used as a diagnostic aid due to the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis
Glucagon	Baqsimi	October 2020	Contraindications	Do not use in patients with pheochromocytoma because of the risk of substantial increase in blood pressure, in patients with insulinoma because of the risk of hypoglycemia and in patients with known hypersensitivity to glucagon or any of the excipients due to reports of anaphylaxis

Randomized Controlled Trials:
A total of 193 citations were manually reviewed from the initial literature search. After further review, 190 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 3 trials are summarized in the evidence table for dasiglucagon (**Table 6**). Full abstracts are included in **Appendix 2**.

NEW DRUG EVALUATION:
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Dasiglucagon works as an antihypoglycemic agent approved for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years or older.[4] Dasiglucagon is available as a ready-to-use product via a prefilled syringe or autoinjector. No reconstitution is required, and dasiglucagon can be stored at room temperature for up to 12 months.[4] Dasiglucagon is a glucagon receptor agonist, which relies on hepatic glycogen to produce the antihypoglycemic effect. Dasiglucagon increases blood glucose concentrations activating hepatic glucagon receptors. This activation results in glycogen breakdown and glucose release from the liver.[4]

Three clinical trials were used for approval of dasiglucagon and are described and evaluated below in **Table 6**. Two trials were conducted in adult patients and had similar trial methodology.[1,2] In the Bailey, et al. trial 44 patients were included in the analysis.[1] The mean age was 41 years, 57% male and 85% white.[1] The mean duration of diabetes was 22.2 years and the mean hemoglobin A1C (A1C) was 7.2%. In the second adult trial (n=170), 92% patients were white with a mean age of 39.1 years and a mean A1C of 7.4%.[2] Baseline characteristics were similar between groups. In both trials, patients were admitted the night before evaluation and fasted the night (starting at 10 pm) before dosing. Insulin was discontinued in advance based on pharmacokinetic profiles (6 to 48 hours). Hypoglycemia was initiated via an IV infusion of glulisine, set to achieve a controlled decline in plasma glucose, with a target plasma glucose level of 55 mg/dL. Glucose levels were monitored bedside every 10 minutes while glucose was above 110 mg/dL and every 5 minutes when glucose levels were at or below 110 mg/dL. Insulin was stopped when glucoses were reduced to 60 mg/dL or less. Glucose levels were measured 5 minutes after insulin was stopped along with baseline laboratory samples for plasma glucose, dasiglucagon and insulin concentrations.[1,2] No more than 2 minutes later, either dasiglucagon or placebo was administered, as long as glucoses fell between 45-60 mg/dL. Glucagon was used as an active control in two trials (1 adult and 1 pediatric).[2,3] Each patient received one dose of dasiglucagon, placebo or glucagon (active control in two trials, no formal statistical comparison). Products were administered SC in the deltoid or buttocks via an autoinjector by trial personnel. Samples were taken at 2 minutes or less before product administration and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 45, 50, 60, 75 and 90 minutes. Safety assessments were pre-dose and at predefined intervals up to 120 and 300 minutes after dose. A safety follow-up was performed 28 days after dosing. The primary endpoint for both trials was the time to plasma glucose recovery, defined as first increase in plasma glucose of 20 mg/dL or higher from baseline without rescue IV glucose.[1,2]

The third trial involved children and adolescents (n=42) who were predominately white with a mean A1C of 7.6% and average age of 13.1 years. The trial allowed for patients as young as 6 years; however, the youngest participant was 7 years. The FDA allowed for data to be extrapolated for approval down to 6 years.[18] Trial methodology was similar to the adult studies with a few exceptions. One dose of dasiglucagon, placebo or glucagon (active control) were given when indicated. The decline in plasma glucose was stopped at 80 mg/dL, higher than adult trials to ensure safety.[3] The study drug was given if the plasma glucose was between 54 mg/dL and less than 80 mg/dL at 5 minutes. If plasma glucose fell outside this range, then insulin or glucose was given to obtain the appropriate glucose concentration.[3] Samples were taken at 2 minutes or less before product administration and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes. A sample was taken at 60 minutes if the patient was 21 kgs or more. Safety follow up was done at screening, dosing visit and follow-up, 28 days after dose.[3]

For the primary endpoint in the adult trials, dasiglucagon raised plasma glucoses to the recovery point in 10 minutes compared to 35-40 minutes for placebo ($p<0.001$).[1,2] Adults treated with glucagon obtained plasma glucose recovery in 12 minutes, with no formal comparison to dasiglucagon.[2] The number of patients who recovered within 15 minutes was higher with dasiglucagon compared to placebo (absolute risk reduction (ARR) 88%-97%/number needed to treat [NNT] 1-2). One patient in the dasiglucagon group required rescue treatment in one trial.[1] Injection site (e.g., abdomen, buttock or thigh) did not influence time to recovery. In children and adolescents, the primary endpoint of glucose recovery for dasiglucagon was 10 minutes, compared to 30 minutes for placebo and 10 minutes for glucagon.[3] Glucose recovery at 15 minutes was higher with dasiglucagon compared to placebo with and ARR of 95% and NNT of 2.[3]

Evidence suggests that dasiglucagon provides clinically relevant increases in plasma glucose and is an effective treatment option for patients with hypoglycemia. No formal analyses compared dasiglucagon to other antihypoglycemic therapies; however, informal comparisons suggest dasiglucagon has similar efficacy to glucagon. There is insufficient data on time to glucose normalization based on delivery system (ready-to-use versus reconstitution). Limitations to trial findings include a small number of patients enrolled, administration by a professional in an inpatient setting, artificial hypoglycemia induction, the evaluation of only one dose of treatment, insufficient evidence in patients 65 years and older and extensive exclusion criteria. The exclusion of patients with concomitant illnesses, which was not defined, also limits applicability to diabetic patients that often have comorbidities. Differences in the number of males in some of the treatment groups was determined by the FDA to be due to the small sample size and was found to have no treatment interaction.[18]

Clinical Safety:
The most commonly reported adverse events in trials were nausea, vomiting and headache.[4] No serious safety concerns were reported. The development of treatment-emergent anti-drug antibodies occurred in less than 1% of dasiglucagon treated patients. Dasiglucagon should not be taken with warfarin, indomethacin or beta-blockers.

Table 3. Dasiglucagon Adverse Reactions Occurring in ≥2% More Frequently than with Placebo in Adults[4]

Adverse Reaction	Placebo (n=53)	Dasiglucagon (n=116)
Nausea	4%	57%
Vomiting	2%	25%
Headache	4%	11%
Diarrhea	0%	5%
Injection site pain	0%	2%

Table 4. Dasiglucagon Adverse Reactions Occurring in ≥2% More Frequently than with Placebo in Pediatric Patients[4]

Adverse Reaction	Placebo (n=11)	Dasiglucagon (n=20)
Nausea	0%	65%
Vomiting	0%	50%
Headache	0%	10%
Injection site pain	0%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Normalization of glucose to 70 mg/dL or more
2) Resolution of hypoglycemia symptoms
3) Mortality
4) Serious adverse events

Primary Study Endpoint:
1) Time to plasma glucose recovery

Table 5. Pharmacology and Pharmacokinetic Properties[4]

Parameter	
Mechanism of Action	Dasiglucagon is an agonist at the glucagon receptor which stimulates hepatic glucagon receptors causing an increase in blood glucose concentrations, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.
Distribution and Protein Binding	Distribution is 47 L to 57 L after subcutaneous injection Protein binding not described
Elimination	Not described
Half-Life	Approximately 30 minutes
Metabolism	Proteolytic degradation pathways in the blood, liver, and kidney

Abbreviations: L = liters

Table 6. 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. Bailey, et al. [1] DB, MC, PC, PG, RCT, Phase 3	1. Dasiglucagon 0.6 mg autoinjector 2. Placebo * Each patient only received one dose of medication or placebo	Demographics: Male: - dasiglucagon 47.1%; - Placebo 90% White: - dasiglucagon 100%; - placebo 70% Mean Age: - dasiglucagon 42.2 years; - placebo 36.5 years HbA1c: - dasiglucagon 7.23%; - placebo 7.18% Plasma glucose: - dasiglucagon 55.1 mg/dL; - placebo 54.6 mg/dL Key Inclusion Criteria: - T1DM ≥1 year - Age 18 to 75 years - Insulin use ≥1 year - HbA1c <10%	ITT: 1. 34 2. 10 Attrition: None	Primary Endpoint: Median time to plasma glucose recovery*: 1. 10.0 minutes 2. 35.0 minutes P < 0.001 (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 30 (88%) 2. 0 P<0.01 (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 33 (97%) 2. 5 (50%) P<0.01 (95% CI NR)	NA ARR 88% /NNT 2 ARR 47% /NNT 3	Nausea: 1. 21 (62%) 2. 1 (10%) Vomiting: 1. 10 (29%) 2. 0 (0%) Headache: 1. 4 (12%) 2. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Patients were randomized 3:1 via interactive web response system. Baseline characteristics were not well matched with may introduce bias. Allocation concealment was maintained by both products being administered via identical autoinjectors. Performance Bias: Unclear. Blinding was maintained via treatment assignments only accessible by authorized personnel. Dasiglucagon and placebo were aqueous formulations in identical autoinjectors. Detection Bias: Unclear. Outcome assessment was not described. Statistical analysis was very limited. Attrition Bias: Low. There was no attrition in either group. Analysis was performed on ITT population. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Severely limited external validity to non-white patients. Forced hypoglycemia with controlled administration was performed in a tightly controlled

		Key Exclusion Criteria: - Clinically significant concomitant illnesses (not described) - Medical histories that could increase early trial withdrawal or potentially confound safety assessment						inpatient setting which does not represent real world scenarios. Intervention: Dasiglucagon 0.6 mg was an appropriate dose as determined by phase 2 studies. Comparator: Placebo comparison was appropriate to determine efficacy but comparison with another glucagon treatment would have provided comparative data. Outcomes: Endpoints were appropriate to determine glucose recovery. Setting: Three inpatient treatment centers in the United States
2. Pieber, et al.[2] DB, MC, PC, PG, RCT, Phase 3	1. Dasiglucagon 0.6 mg autoinjector 2. Placebo 3. Glucagon 1 mg (reconstituted)† * Each patient only received one dose of medication or placebo	Demographics: Male: 63% White: 92% Mean Age: 37 years Mean HbA1c: 7.4% Mean Plasma glucose: 58.7 mg/dL Key Inclusion Criteria: - Same as above Key Exclusion Criteria: - Hypoglycemia with seizure in preceding year - Severe hypoglycemia during previous month - Use of beta-blockers, warfarin, indomethacin or anticholinergics drugs daily during previous 28 days	ITT: 1. 82 2. 43 3. 43 Attrition: None	Primary Endpoint: Time to plasma glucose recovery*: 1. 10.0 minutes 2. 40.0 minutes 3. 12 minutes P<0.001 (relative to placebo) (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 81 (99%) 2. 1 (2%) 3. 41 (95%) P<0.001 (relative to placebo) (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 82 (100%) 2. 20 (47%) 3. 43 (100%) P<0.001 (relative to placebo) (95% CI NR)	NA ARR 97% /NNT 1 ARR 53% / NNT 2	Nausea: 1. 45 (55%) 2. 1 (2%) 3. 23 (53%) Vomiting: 1. 19 (23%) 2. 1 (2%) 3. 9 (21%) Headache: 1. 8 (10%) 2. 1 (2%) 3. 4 (9%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 2:1:1 via an interactive web response system. Baseline characteristics were well matched. Performance Bias: High. Medications were different in appearance. Administration was provided by unblinded trial personnel who were not involved in other trial activities. Detection Bias: Unclear. No details on outcome assessment were provided. Limited statistics provided. Attrition Bias: Low. No missing data. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Results are most applicable to younger, white adults. Intervention: Dasiglucagon was an appropriate dose. Comparator: Comparative analysis between dasiglucagon and glucagon would provide data for place in therapy. Outcomes: Outcomes were appropriate to determine glucose recovery. Setting: Germany (2), Austria (1), United States (1) and Canada (1)
3. Battelino, et al. [3]	1. Dasiglucagon 0.6 mg 2. Placebo 3. GlucaGen†	Demographics: Male: 32% White: 93% Mean Age: - dasiglucagon 12.5 years; - placebo 15.0 years;	FAS: 1. 20 2. 11 3. 10 PP:	Primary Endpoint: Time to plasma glucose recovery*: 1. 10 minutes 2. 30 minutes 3. 10 minutes		Nausea: 1. 13 (65%) 2. 0 (0%) 3. 3 (30%) Vomiting:	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 2:1:1 via a central, dynamic variance minimization randomization method via an interactive web response system. Baseline characteristics were well matched with the

DB, MC, PC, PG, RCT, Phase 3	* Each patient only received one dose of medication or placebo	- GlucaGen 12.0 years HbA1c: 7.6% Plasma glucose: 72.64 mg/dL Key Inclusion Criteria: - Age 6-17 years - T1DM for ≥1 year - Receiving daily insulin - Body weight ≥20 kg Key Exclusion Criteria: -Insulinoma or pheochromocytoma - Hypoglycemia with seizures or hypoglycemia unawareness (as assessed at the investigator's discretion) in the prior year - Severe hypoglycemia in prior month - Use of beta-blockers, warfarin, indomethacin, anticholinergics or medication known to prolong the QT interval during previous 28 days prior to screening	1. 19 2. 10 3. 9 Attrition: 1. 1 (5%) 2. 1 (9%) 3. 1 (10%)	P<0.001 (relative to placebo) (95% CI NR) Secondary Endpoints: Percent of patients achieving glucose recovery within 15 min: 1. 19 (95%) 2. 0 (0%) 3. 10 (100%) P<0.001 (relative to placebo) (95% CI NR) Percent of patients achieving glucose recovery within 30 min: 1. 20 (100%) 2. 6 (55%) 3. 10 (100%) P=0.007 (relative to placebo) (95% CI NR)	NA ARR 95% / NNT 2 ARR 45% / NNT 3	1. 10 (50%) 2. 0 (0%) 3. 1 (10%) Headache: 1. 2 (10%) 2. 1 (9.1%) 3. 1 (10%)		exception of a higher average age in the placebo group compared to the other treatment groups. Performance Bias: High. Medications were different in appearance. Administration was provided by unblinded trial personnel who were not involved in other trial activities. Detection Bias: Unclear. No details on outcome assessment were provided. Statistical analysis was very limited. Attrition Bias: Low. Attrition was 10% or less. Reporting Bias: Low. Outcomes were reported as described. Other Bias: High. Manufacturer funded study. **Applicability**: Patient: Results are most applicable to children and adolescents 12 and older who are white. Intervention: Dasiglucagon was an appropriate dose as determined in phase 2 studies. Comparator: Comparative analysis between dasiglucagon and GlucaGen would provide data for place in therapy. Outcomes: Outcomes were appropriate to determine glucose recovery. Setting: Five sites in Germany, Slovenia, and the United States

Abbreviations: ARR = absolute risk reduction; DB = double-blind; CI = confidence interval; HbA1c = hemoglobin A1c; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NR = not reported; NNH = number needed to harm; NNT = number needed to treat; PG = parallel group; PP = per protocol; T1DM = Type 1 Diabetes Mellitus
Key: * Defined as a plasma glucose increase of 20 mg/dL or higher from baseline without rescue intravenous glucose; † Active control; ‡ Confidence intervals not provided

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
glucagon	BAQSIMI	SPRAY	NS	Y
glucagon	GLUCAGEN	VIAL	IJ	Y
glucagon	GLUCAGON EMERGENCY KIT	VIAL	IJ	Y
dasiglucagon HCl	ZEGALOGUE AUTOINJECTOR	AUTO INJCT	SQ	N
dasiglucagon HCl	ZEGALOGUE SYRINGE	SYRINGE	SQ	N
glucagon	GVOKE HYPOPEN 1-PACK	AUTO INJCT	SQ	N
glucagon	GVOKE HYPOPEN 2-PACK	AUTO INJCT	SQ	N
glucagon	GVOKE PFS 1-PACK SYRINGE	SYRINGE	SQ	N
glucagon	GVOKE PFS 2-PACK SYRINGE	SYRINGE	SQ	N
glucagon HCl	GLUCAGON EMERGENCY KIT	VIAL	IJ	
glucagon HCl	GLUCAGON HCL	VIAL	IJ	

Appendix 2: Abstracts of Comparative Clinical Trials

Dasiglucagon, a next-generation glucagon analogue, for treatment of severe hypoglycemia via an autoinjector device: Results of a phase 3, randomized, double-blind trial
Bailey TS, Willard J, Klaff LJ, Yager Stone J, Melgaard A, et al.

Abstract
Aim: To confirm the efficacy and safety of dasiglucagon when administered via an autoinjector device.
Materials and methods: In this double-blind trial, 45 participants with type 1 diabetes were randomized 3:1 to receive a single subcutaneous dose of dasiglucagon 0.6 mg or placebo following controlled induction of hypoglycaemia. The primary endpoint was time to plasma glucose recovery, defined as a plasma glucose increase of 20 mg/dL or higher from baseline without rescue intravenous glucose.
Results: Median (95% CI) observed time to recovery was 10.0 (8.0; 12.0) minutes for dasiglucagon and 35.0 (20.0; -) minutes for placebo (P < .001). Plasma glucose recovery was achieved within 15 minutes by 88% of participants receiving dasiglucagon versus none receiving placebo (P < .01). Site of injection (buttock

or deltoid) was not shown to have any effect on time to recovery (P = .84). No serious adverse events occurred. As expected for glucagon treatment, nausea and vomiting were common adverse events in dasiglucagon-treated participants.
Conclusions: Dasiglucagon provided rapid reversal of hypoglycaemia in adults with type 1 diabetes. Dasiglucagon administration was well tolerated. The aqueous formulation of dasiglucagon in a ready-to-use autoinjector device that can be carried at room temperature may provide a reliable treatment for severe hypoglycaemia.

Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: Results of a phase 3, randomized controlled trial
Battelino T, Tehranchi R, Bailey T, Dovc K, Melgaard A, et al.

Abstract
Background: Dasiglucagon, a next-generation, ready-to-use aqueous glucagon analog formulation, has been developed to treat severe hypoglycemia in individuals with diabetes.
Objective: The aim of this trial was to evaluate the safety and efficacy of dasiglucagon in pediatric individuals with type 1 diabetes (T1DM). Participants were children and adolescents (6-17 years) with T1DM.
Methods: In this randomized double-blind trial, 42 participants were randomly allocated (2:1:1) to a single subcutaneous (SC) injection of dasiglucagon (0.6 mg), placebo, or reconstituted glucagon (GlucaGen; dosed per label) during insulin-induced hypoglycemia. The primary endpoint was time to plasma glucose (PG) recovery (first PG increase ≥20 mg/dL after treatment initiation without rescue intravenous glucose). The primary comparison was dasiglucagon vs. placebo; glucagon acted as a reference.
Results: The median time (95% confidence interval) to PG recovery following SC injection was 10 min (8-12) for dasiglucagon vs. 30 min (20 to -) for placebo (P < .001); the median time for glucagon was 10 min (8-12), which did not include the time taken to reconstitute the lyophilized powder. PG recovery was achieved in all participants in the dasiglucagon and glucagon groups within 20 min of dosing compared to 2 out of 11 patients (18%) with placebo. The most frequent adverse events were nausea and vomiting, as expected with glucagon treatment.
Conclusions: Consistent with adult phase 3 trials, dasiglucagon rapidly and effectively restored PG levels following insulin-induced hypoglycemia in children and adolescents with T1DM, with an overall safety profile similar to glucagon.

Dasiglucagon: A Next-Generation Glucagon Analog for Rapid and Effective Treatment of Severe Hypoglycemia Results of Phase 3 Randomized Double-Blind Clinical Trial
Pieber T, Aronson R , Hövelmann U, Willard J, et al

Abstract
Objective: To evaluate the efficacy and safety of dasiglucagon, a ready-to-use, next-generation glucagon analog in aqueous formulation for subcutaneous dosing, for treatment of severe hypoglycemia in adults with type 1 diabetes.
Research Design and Methods: This randomized, double-blind trial included 170 adult participants with type 1 diabetes, each randomly assigned to receive a single subcutaneous dose of 0.6 mg dasiglucagon, placebo, or 1 mg reconstituted glucagon (2:1:1 randomization) during controlled insulin-induced hypoglycemia. The primary end point was time to plasma glucose recovery, defined as an increase of ≥20 mg/dL from baseline without rescue intravenous glucose. The primary comparison was dasiglucagon versus placebo; reconstituted lyophilized glucagon was included as reference.

Results: Median (95% CI) time to recovery was 10 (10, 10) minutes for dasiglucagon compared with 40 (30, 40) minutes for placebo ($P < 0.001$); the corresponding result for reconstituted glucagon was 12 (10, 12) minutes. In the dasiglucagon group, plasma glucose recovery was achieved within 15 min in all but one participant (99%), superior to placebo (2%; $P < 0.001$) and similar to glucagon (95%). Similar outcomes were observed for the other investigated time points at 10, 20, and 30 min after dosing. The most frequent adverse effects were nausea and vomiting, as expected with glucagon treatment.
Conclusions: Dasiglucagon provided rapid and effective reversal of hypoglycemia in adults with type 1 diabetes, with safety and tolerability similar to those reported for reconstituted glucagon injection. The ready-to-use, aqueous formulation of dasiglucagon offers the potential to provide rapid and reliable treatment of severe hypoglycemia.

Appendix 3: Medline Search Strategy
Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 06, 2021
Search Strategy:

#	Searches	Results
1	Glucagon/ or glucagon.mp.	49923
2	dasiglucagon.mp.	16
3	1 or 2	49927
4	limit 3 to (english language and humans and yr="2019 -Current")	2494
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	193

Appendix 4: Prescribing Information Highlights

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

ZEGALOGUE (dasiglucagon) injection, for subcutaneous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

ZEGALOGUE is an antihypoglycemic agent indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above. (1)

DOSAGE AND ADMINISTRATION

- ZEGALOGUE autoinjector and prefilled syringe are for subcutaneous injection only. (2.1)
- The dose in adults and pediatric patients aged 6 years and older is 0.6 mg. (2.2)
- Administer ZEGALOGUE according to the printed instructions on the protective case label and the Instructions For Use. (2.1)
- Visually inspect ZEGALOGUE prior to administration. The solution should appear clear, colorless, and free from particles. If the solution is discolored or contains particulate matter, do not use. (2.1)
- Administer the injection into the lower abdomen, buttocks, thigh, or outer upper arm. (2.1)
- Call for emergency assistance immediately after administering the dose. (2.1)
- If there has been no response after 15 minutes, an additional dose of ZEGALOGUE from a new device may be administered while waiting for emergency assistance. (2.1)
- When the patient has responded to treatment, give oral carbohydrates. (2.1)
- Do not attempt to reuse ZEGALOGUE. Each device contains a single dose of dasiglucagon and cannot be reused. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection:

- 0.6 mg/0.6 mL single-dose autoinjector (3)
- 0.6 mg/0.6 mL single-dose prefilled syringe (3)

CONTRAINDICATIONS

Pheochromocytoma (4)
Insulinoma (4)

WARNINGS AND PRECAUTIONS

- *Substantial Increase in Blood Pressure in Patients with Pheochromocytoma:* Contraindicated in patients with pheochromocytoma because ZEGALOGUE may stimulate the release of catecholamines from the tumor. (4, 5.1)
- *Hypoglycemia in Patients with Insulinoma:* In patients with insulinoma, administration may produce an initial increase in blood glucose, but ZEGALOGUE may stimulate exaggerated insulin release from an insulinoma and cause subsequent hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of ZEGALOGUE, give glucose orally or intravenously. (4, 5.2)
- *Hypersensitivity and Allergic Reactions:* Allergic reactions have been reported with glucagon products and may include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. (5.3)
- *Lack of Efficacy in Patients with Decreased Hepatic Glycogen:* ZEGALOGUE is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for ZEGALOGUE to be effective. Patients with these conditions should be treated with glucose. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) associated with ZEGALOGUE are:
Adults: nausea, vomiting, headache, diarrhea, and injection site pain
Pediatrics: nausea, vomiting, headache, and injection site pain (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Zealand Pharma A/S at 1-877-501-9342or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- *Beta-blockers:* Patients taking beta-blockers may have a transient increase in pulse and blood pressure. (7)
- *Indomethacin:* In patients taking indomethacin, ZEGALOGUE may lose its ability to raise blood glucose or may produce hypoglycemia. (7)
- *Warfarin:* ZEGALOGUE may increase the anticoagulant effect of warfarin. (7)

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

Revised 03/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with type 1 or type 2 diabetes
Intervention	Glucagon therapies (e.g., spray, vial, auto-injector)
Comparator	Placebo or active control
Outcomes	Normalization of glucose levels to 70 mg/dL or above, increase in glucose levels of at least 20 mg/dL and resolution of hypoglycemia symptoms
Timing	As needed for hypoglycemia
Setting	Outpatient

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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Drug Class Update with New Drug Evaluation: Drugs for Paroxysmal Nocturnal Hemoglobinuria

Date of Review: December 2021

Date of Last Review: April 2021
Dates of Literature Search: 01/01/2020 – 07/20/2021

Generic Name: Pegcetacoplan

Brand Name (Manufacturer): EMPAVELI
Dossier Received: yes

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

Purpose for Class Update:
To define place in therapy for a new immunosuppressive agent, pegcetacoplan, which is Food and Drug Administration (FDA)-approved for treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). In addition, assess recently published evidence for 2 additional agents, eculizumab and ravulizumab, which are also indicated for management of PNH.

Research Questions:
1. What is the comparative efficacy or effectiveness of drugs indicated for the treatment of PNH in adults?
2. What are the comparative harms of drugs indicated for the treatment of PNH in adults?
3. Are there certain sub-populations (based on age, gender, race, ethnicity, comorbidities, disease duration or severity) in which pegcetacoplan, eculizumab or ravulizumab may be beneficial or cause more harm in adults with PNH?

Conclusions:
Pegcetacoplan
- The safety and efficacy of pegcetacoplan were evaluated in a 48-week, prospective, randomized, multicenter, open-label, active-comparator controlled trial (PEGASUS).[1] During the 16-week randomized phase of the study, pegcetacoplan was compared with eculizumab in 80 adults with PNH who continued to have hemoglobin levels less than 10.5 g/dL despite treatment with eculizumab.[1] The open-label study design of the trial introduced risk for performance and detection biases.
- The primary efficacy endpoint in the trial was change from baseline in hemoglobin level at week 16.[1] During 16 weeks of treatment, patients in the pegcetacoplan group had an adjusted least squares (LS) mean change from baseline increase in their hemoglobin of 2.4 g/dL, while patients in the eculizumab group had an average decrease in their hemoglobin of 1.5 g/dL; with an LS mean difference of 3.84 g/dL (95% confidence interval [CI], 2.33 to 5.34; P<0.0001), based on low quality evidence.[1]

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- Key secondary endpoints were the proportion of patients who did not require a transfusion during the randomized, controlled period and the change from baseline to week 16 in absolute reticulocyte count (ARC), lactate dehydrogenase (LDH) level, and score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale.[1] Low-quality evidence showed pegcetacoplan met noninferiority to eculizumab on transfusion avoidance (pegcetacoplan: 85% patients vs. eculizumab 15% patients; difference, 62.5%; 95% CI 48.3 to 76.8%).[1] Pegcetacoplan was also noninferior to eculizumab for change in ARC, based on low quality evidence (pegcetacoplan –135.8 vs. eculizumab 27.8; LS mean difference -163.6×10^9 cells/L; 95% CI, -189.9 to -137.3×10^9 cells/L).[1] For change in LDH level, the adjusted mean change from baseline was −15 U/L in the pegcetacoplan group and −10 U/L in the eculizumab group and the noninferiority criterion of -20 U/L change was not met.[1] Scores on the FACIT-F scale were not tested for noninferiority because the between-group difference in LDH level did not meet the noninferiority criterion, thereby causing a break in the hierarchal testing strategy.[1]
- The most common adverse events that occurred during 16-week treatment in the pegcetacoplan and eculizumab groups, respectively, were injection site reactions (39% vs. 3%), infections (29% vs. 26%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (12% vs. 23%).[1] Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. There are insufficient data to assess the long-term safety of pegcetacoplan.
- Serious infections can occur in patients taking pegcetacoplan that can become life-threatening or fatal if not treated early.[2] Pegcetacoplan is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) because of the risk of severe side effects.[2]
- There is insufficient evidence to evaluate the use of pegcetacoplan in the treatment of specific subpopulations based on age, gender, race, ethnicity, comorbidities, disease duration or severity.

Eculizumab/Ravulizumab

- National Institute for Health and Care Excellence (NICE) guidance for the use of ravulizumab for treating PNH was issued May 2021.[3] Ravulizumab is recommended as an option for treating PNH in adults: 1) with hemolysis and clinical symptoms suggesting high disease activity, or 2) whose disease is clinically stable after receiving eculizumab for at least 6 months.[3]
- In June 2021 the FDA expanded the approved indications for ravulizumab to include treatment of pediatric patients one month of age and older and weighing 5 kg or greater with PNH and atypical hemolytic-uremic syndrome (aHUS).[4] Ravulizumab was previously approved only for use in adults with PNH or aHUS and pediatric patients less than 18 years of age with aHUS.
- No new head-to-head trials have been published to evaluate the comparative safety and efficacy of eculizumab, ravulizumab or pegcetacoplan therefore comparative evidence remains insufficient.

Recommendations:

- Revise ravulizumab prior authorization (PA) criteria to reflect expanded indication for use in pediatric patients aged 1 month and older with PNH or aHUS. Revise dosing (**Table 1)** to reflect updated indications.
- Add pegcetacoplan to the "Biologics for Rare Diseases" drug class on the Preferred Drug List (PDL).
- Implement clinical prior authorization criteria for pegcetacoplan (**Appendix 4**) to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (OHP).
- Review costs in Executive Session.

Summary of Prior Reviews and Current Policy

At the April 2021 Pharmacy & Therapeutics (P & T) Committee meeting, the P & T Committee reviewed evidence supporting the FDA approval of eculizumab and ravulizumab for the treatment of PNH. A new class of drugs entitled "Biologics for Rare Diseases" was added to the Preferred Drug List (PDL). Eculizumab and

ravulizumab were included in this new PDL class. To ensure appropriate utilization in FDA-approved indications funded by OHP, clinical PA criteria were implemented for eculizumab and ravulizumab (**Appendix 4**). Besides PNH, eculizumab is FDA-approved for 3 additional indications including: 1) inhibiting complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS, 2) managing generalized myasthenia gravis (MG) and 3) treatment of adults with neuromyelitis optica spectrum disorder (NMOSD).[5] Ravulizumab is also FDA-approved for treatment of aHUS.[4] After executive session, ravulizumab was designated as a preferred agent on the PDL and eculizumab was designated as non-preferred. Other monoclonal antibodies that are included in the Biologic for Rare Diseases class are listed in **Appendix 1**. In the first quarter of 2021, 2 claims in Fee-for-Service (FFS) population were submitted for eculizumab. No claims were received for other drugs in the Biologics for Rare Disease drug class.

Background:

Paroxysmal nocturnal hemoglobinuria is a rare disease characterized by uncontrolled complement activation, which leads to a variety of symptoms, including hemolytic anemia, fatigue, and shortness of breath.[6] Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.[6] PNH results from the expansion of abnormal hematopoietic clones that lack cell-surface complement inhibitory proteins attached to the membrane through glycosylphosphatidylinositol anchors.[7] The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.[6] The condition is genetic, with the mutations occurring on the X-linked gene.[6] This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes.[6] Proteins responsible for the regulation of complement activity, specifically CD55 and CD59, are thereby prevented from attaching to affected cells.[6] This leads to activation of C3, C5, and the terminal pathway of complement culminating in the formation of the membrane attack complex (MAC).[8] Under normal conditions, formation of the MAC is under the regulation of CD59.[8] The absence of CD59 on erythrocytes leads to uncontrolled formation of the MAC resulting in complement-mediated intravascular hemolysis.[8] This chronic state of hemolysis can be exacerbated if the complement system is activated by stress due to surgery, trauma, infection, or other triggers for inflammation.[6] As a result of intravascular hemolysis, the circulating levels of LDH are increased. Lactate dehydrogenase is released upon cell or tissue damage, and an elevated serum LDH level is a measure of erythrocyte injury from ongoing hemolysis.[9] In patients with PNH, LDH is usually elevated and used both as a diagnostic tool and to monitor the severity of hemolysis.[9] LDH levels can be up to 10-times the upper limit of normal (ULN) in untreated PNH.[8] Patients with hemolytic PNH have an average LDH level of 2,201 ± 105 U/L, compared with the normal LDH range of 103 to 223 U/L.[8]

Anemia in PNH is often multifactorial and may result from a combination of hemolysis and bone marrow failure.[8] Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in LDH is common in classic PNH.[8] Patients with classic PNH often have a high percentage of PNH granulocytes (greater than 50%).[8] PNH in the context of other primary marrow disorders usually refers to acquired aplastic anemia.[8] Thrombosis leads to severe morbidity and is the most common cause of mortality in PNH.[8] Thrombosis in PNH may occur at any site; however, venous thrombosis is more common than arterial thrombosis.[8] Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of hemolysis and the release of free hemoglobin.[8] Free hemoglobin is normally cleared by haptoglobin, CD163, and hemopexin.[8] These clearing mechanisms are overwhelmed in PNH and lead to accumulation of high levels of free hemoglobin in the plasma and consequently, depletion of nitric oxide.[8] Renal tubular damage is caused by microvascular thrombosis and accumulation of iron deposits. Raised pulmonary pressures and reduced right ventricular function caused by subclinical microthrombi and hemolysis-associated nitric oxide scavenging contribute to symptoms of fatigue and dyspnea.[8] A classification scheme, proposed by the International PNH Interest Group, includes 3 main categories of PNH: (1) classic PNH, which includes hemolytic and thrombotic patients; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have clones, but no clinical or laboratory evidence of hemolysis or thrombosis.[10] This

classification scheme has resulted in some confusion because varying degrees of bone marrow failure underlie virtually all cases of PNH; thus, the distinction between 3 categories may be difficult in some cases.[8]

PNH is rare, with occurrence estimated as 15.9 individuals per million worldwide.[11] Some authors indicate that this number is probably low as the disease remains undiagnosed in individuals with limited symptomatology, or with comorbid conditions that obscure the PNH diagnosis.[12] Typically most patients are diagnosed at 30 years to 40 years of age.[6] Children can be affected by PNH, but it is uncommon.[6] According to an analysis of 1,610 patients registered in the International PNH Registry in 2012, the median age of all registered patients was 42 years, with the disease duration of 4.6 years.[13] The age range of patients in the registry was 3 to 99 years.[13] While the occurrence of PNH has no apparent ethnic or geographic distribution, there is an increased risk of thrombosis in the United States (US) and Europe.[6] About 30 to 40% of PNH cases are reported in the US and Europe, whereas less than 10% of PNH cases are reported from Asia.[6] Consequently, the incidence of thromboembolism due to PNH is higher in the US and Europe compared to Japan.[14] Patients affected by PNH in the US demonstrate differences in complications according to ethnic groups. African-Americans with PNH have a 73% incidence of thromboembolism and Latin Americans have about a 50% incidence.[6] White and Asian Americans have a 36% incidence of thromboembolism complications.[6] Bone marrow failure also varies with ethnicity and geography.[6] It is more common in residents of Asia, the Pacific Islands, and Latin America.[6] The reasons for these variations are not clear.[6]

In the past, PNH treatment was mostly supportive.[6] Patients were given a blood transfusion and iron supplementation for anemia from recurrent hemolysis and anti-thrombosis prophylaxis was initiated to prevent thrombosis.[6] For severe, life-threatening bone marrow complications, an allogeneic bone marrow transplant was offered.[6] The mainstay of current therapy for PNH includes the C5 inhibitors eculizumab and ravulizumab.[6] These agents prevent cleavage and the formation of the MAC which averts complement-mediated intravascular hemolysis. Although C5 inhibitor therapies control intravascular hemolysis and have improved the disease trajectory for patients with PNH, some patients continue to have suboptimal C5 blockade, resulting in a potential risk of continued extravascular hemolysis, elevated LDH, and sustained risk of thromboembolic events.[8] Surviving PNH erythrocytes become opsonized with C3 fragments and are removed by extravascular hemolysis in the liver and spleen.[1] Extravascular hemolysis is observed in most patients with PNH who are being treated with C5 inhibitors and leads to reduced erythrocyte half-life (10 to 13 days).[1] Low hemoglobin levels, elevated reticulocyte counts, elevated bilirubin levels, continued need for red blood cell (RBC) transfusions, and persistent patient-reported fatigue are indicators of ongoing disease activity despite treatment with C5 inhibitors.[15] Other novel therapy development projects are focusing on targets upstream in the complement pathway, such as C1, C3, and Factor D inhibitors.[6]

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

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

Systematic Reviews: No new systematic reviews have been published since the last class update.

New Guidelines:
High Quality Guidelines
National Institute for Health and Care Excellence
NICE guidance for the use of ravulizumab in treating PNH was issued May 2021.[3] Paroxysmal nocturnal hemoglobinuria is currently treated with eculizumab infusions every 2 weeks. Clinical trial evidence shows that ravulizumab and eculizumab are similarly safe and effective.[3] Ravulizumab is administered less often than eculizumab. Ravulizumab is recommended as an option for treating PNH in adults when: 1) hemolysis and clinical symptoms suggest high disease activity, or 2) disease is clinically stable after eculizumab treatment for at least 6 months.[3]

New Formulations or Indications:
In June 2021, the FDA expanded the approved indications for ravulizumab to treatment of pediatric patients one month of age and older and weighing 5 kg or greater with PNH and aHUS.[4] Ravulizumab was previously approved only for use in adults with PNH or aHUS and pediatric patients less than 18 years of age with aHUS. The expanded pediatric indication was based upon extrapolation of evidence from RCTs in adults and patients aged 9 to 17 years.[4] The manufacturer of ravulizumab, Alexion Pharmaceuticals, supplies the product in 2 concentrations: 100 mg/mL and 10 mg/mL.[4]

New FDA Safety Alerts: No new safety alerts focused on eculizumab or ravulizumab have been issued in the past year.

Randomized Controlled Trials:
A total of 5 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Pegcetacoplan
See **Appendix 3** 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:
Pegcetacoplan received FDA approval May 2021 for the treatment of adult patients with PNH.[2] Pegcetacoplan binds to complement protein C3, which prevents intravascular and extravascular hemolysis.[1] In contrast, protein C5 inhibition only targets intravascular hemolysis. The recommended pegcetacoplan dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump.[2] Pegcetacoplan is intended for use under the guidance of a healthcare professional (HCP).[2] After proper training, a patient may self-administer the drug, or the patient's caregiver may administer pegcetacoplan if the HCP determines that is appropriate.[2]

Pegcetacoplan was approved based upon results from the phase 3 PEGASUS study and two phase 2 trials in patients naïve to anti-complement therapy.[16] The PEGASUS study details are described and evaluated below in **Table 4.** PEGASUS was a 48-week randomized, multicenter, open-label, active-comparator controlled study that evaluated the efficacy and safety of pegcetacoplan compared with eculizumab in 80 adults with PNH who continued to have hemoglobin levels less than 10.5 g/dL despite treatment with eculizumab.[1] The treatment period of the study consisted of three parts: 1) a 4-week run-in period in which patients received both pegcetacoplan and their current eculizumab dose, 2) a 16-week randomized controlled period in which patients were randomized to receive either pegcetacoplan or eculizumab monotherapy, and 3) a 32-week open-label pegcetacoplan-only period. The 4 week run-in period was for safety

purposes to avoid abruptly switching patients from eculizumab to pegcetacoplan. Patients were randomized 1:1 to receive either 1,080 mg of pegcetacoplan twice weekly (n=41) or their current dosage of eculizumab (n=39) during the 16-week randomized controlled period.[1] If a patient did not respond sufficiently to the twice weekly dosing regimen (LDH greater than 2-times the ULN), the dose of pegcetacoplan could be adjusted to 1,080 mg every 3 days.[1] In the pegcetacoplan arm, 2 patients required every 3-day dosing.[1]

Treatment groups were generally balanced with regard to baseline characteristics, including transfusions in the previous 12 months and baseline hemoglobin levels (~8.7 g/dL in both groups).[1] The most common eculizumab dosing regimen was 900 mg every 2 weeks (70% of patients), consistent with the FDA-approved label.[1] Thirty percent of patients on eculizumab were on a dose greater than the FDA-approved dose.[1] Specifically, these patients received 1,200 mg every 2 weeks (26.3%), 1,500 mg every 2 weeks (2.5%), or 900 mg every 11 days (1.3%).[1] If a patient required a transfusion during the 16-week randomized period, their data collected after the transfusion was excluded from descriptive statistics for all efficacy endpoints.[1] If a patient discontinued study treatment, any values collected after discontinuation continued to be used in analyses.[1] Data from patients who withdrew from the study were handled in the same manner as for patients who received transfusions.[1]

The primary efficacy endpoint was change from baseline in hemoglobin level at week 16 after randomization to pegcetacoplan or eculizuamb.[1] The between-treatment group comparison for the primary efficacy endpoint was performed using a mixed-effect model for repeated measures.[1] Pegcetacoplan was superior to eculizumab with regard to change from baseline in hemoglobin level: the adjusted LS mean change from baseline was 2.4 g/dL for pegcetacoplan and −1.5 g/dL for eculizumab, with an adjusted LS mean difference of 3.84 g/dL (95% CI, 2.33 to 5.34; P<0.0001).[1]

Key secondary end points were the proportion of patients who did not require a transfusion during the 16 week randomized period and the change from baseline to week 16 in ARC, LDH level, and score on the FACIT-F scale (scores range from 0 to 52, with higher scores indicating less fatigue).[1] A FACIT-F score of 43.6 is considered normal for a healthy adult.[1] Secondary end-point analyses were based on hierarchal assessments and prespecified noninferiority margins.[1] For the proportion of patients who avoided transfusions, if the lower bound of the 95% CI for the difference was greater than the noninferiority margin of –20%, pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in ARC.[1] For the change in ARC, if the upper bound of the 95% CI for the difference between the treatment groups was less than the noninferiority margin of 10×10^9/L, pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in LDH level.[1] For the change in LDH from baseline to week 16, if the upper bound of the 95% CI for the difference between the treatment groups was less than the noninferiority margin of 20 U/L, pegcetacoplan was considered noninferior to eculizumab and testing proceeded with the 16-week change in FACIT-F score.[1]

Pegcetacoplan was noninferior to eculizumab in transfusion avoidance and ARC.[1] Eighty-five percent of pegcetacoplan patients and 15% of eculizumab patients were transfusion-free over the 16-week randomized controlled period (difference: 62.5%; 95% CI 48.3 to 76.8%).[1] The change at 16 weeks from baseline in ARC was -136×10^9 cells/L for pegcetacoplan and 28×10^9 cells/L for eculizumab arms with an LS mean difference of -163.6×10^9 cells/L (95% CI -189.9×10^9 cells/L to -137.3×10^9 cells/L).[1] For change at 16 weeks from baseline in the endpoint of LDH level, the noninferiority criterion of -20 U/L change was not met; the adjusted mean change from baseline was −15 U/L in the pegcetacoplan group and −10 U/L in the eculizumab group.[1] Changes in fatigue levels as measured by the FACIT-F scale, were not tested for noninferiority because the between-group difference in LDH level did not meet the noninferiority criterion, thereby causing a break in the hierarchal testing strategy.[1] FACIT-F scores increased with pegcetacoplan by 9.2 points and decreased with eculizumab by 2.7 points.[1] A 3-point change in FACIT-F score is considered clinically significant.[1] The adjusted mean difference in FACIT-Fatigue scores between pegcetacoplan and eculizumab was 11.9 points (95% CI, 5.49-18.25) at 16 weeks.[1] These are numerical differences, and no comparisons can be drawn between the two arms.[1]

The Pegasus study has several biases that impact the quality of the data. The study population was limited to a subset of patients with PNH with a hemoglobin level of less than 10.5 g/dL despite 3 months of eculizumab treatment. Data from this trial cannot be extrapolated to treatment-naïve adults. The study was not double-blinded for patients or investigators, and the open-label trial design does not exclude the potential for performance or detection bias.[1] Differences in underlying disease severity may have played a role in a small subgroup of patients (n=2) who required dose adjustments in pegcetacoplan after cessation of eculizumab.[1] The PRINCE study, a phase 3 open-label, multicenter, randomized, controlled study is currently ongoing. The study is evaluating the efficacy and safety of pegcetacoplan in adults with PNH who are C5 treatment-naïve. The results of this study will be reported upon study completion.

Clinical Safety:
The most common adverse events that occurred during treatment over 16 weeks in the pegcetacoplan and eculizumab groups, respectively, were injection site reactions (39% vs. 5%), infections (29% vs. 26%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (12% vs. 23%).[1] The majority of injection-site reactions were mild and occurred early in the trial; none resulted in discontinuation.[1] Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan.[2] One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines.[2] Long term safety data for pegcetacoplan is insufficient. The adverse reactions reported during the PEGASUS trial are summarized in **Table 2**.

Table 2. Adverse Reactions Reported In 5% Or More Of Patients Treated With Pegcetacoplan Compared With Eculizumab[2]

Adverse Reactions	Pegcetacoplan n=41	Eculizumab n=39
Injection-site reaction	39%	5%
Infections	29%	26%
Diarrhea	22%	3%
Abdominal Pain	20%	10%
Respiratory tract infection	15%	13%
Viral Infection	12%	8%
Fatigue	12%	23%
Back Pain	7%	10%
Chest Pain	7%	3%
Headache	7%	23%
Hypertension	7%	3%

Due to complement inhibition, meningococcal infections may occur in patients treated with pegcetacoplan and may become rapidly life-threatening or fatal if not recognized and treated early.[2] Use of pegcetacoplan may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B.[2] There were no cases of meningitis reported in either treatment arm of the PEGASUS trial.[1] Patients were vaccinated against encapsulated bacteria prior to study enrollment to reduce the risk of serious infection.[1] Pegcetacoplan is available only through a restricted REMS program. An FDA black boxed warning in the manufacturer's prescribing information contains the following guidance:

• Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients with altered immunocompetence associated with complement deficiencies.[2]
• Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of pegcetacoplan unless the risks of delaying therapy with pegcetacoplan outweigh the risk of developing a serious infection.[2]
• Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.[2]

Look-alike / Sound-alike Error Risk Potential: No issues have been reported.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Decrease hemolysis as measured by change in LDH level
2) Stabilize anemia requiring blood transfusions
3) Reduce fatigue that impacts quality of life
4) Improve survival
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in hemoglobin level from baseline to week 16

Table 3. Pharmacology and Pharmacokinetic Properties[2]

Parameter	
Mechanism of Action	Complement protein C3 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 3.9 L; Protein Binding N/R
Elimination	Clearance is 0.37 L/day
Half-Life	8 days
Metabolism	Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathway

Abbreviations: L=Liters; N/A=not applicable; N/R=not reported

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. Hillmen P, et al.[1] Phase 3 OL, MC, AC RCT	1. Pegcetacoplan 1080 mg SC infusion twice weekly 2. Eculizumab 900 mg IV infusion every 2 weeks or dose being used upon study entry 4 week run-in period: both drugs administered to all study participants 16 week randomized controlled period: each drug administered to assigned arm as monotherapy 32 week open-label, single-arm period in which all subjects received pegcetacoplan	Demographics: -Mean age: 48.8 y -Female: 61% -White: 61% -No transfusions last 12 mo: 25% -Mean Hgb level: 8.7 g/dL -Mean LDH level: Pegcetacoplan: 257.5 U/L Eculizumab: 308.6 U/L Key Inclusion Criteria: -Adults ≥ 18 y diagnosed with PNH -Hgb level < 10.5 g/dL despite ≥ 3 months of eculizumab -BMI < 35 kg/m^2 -Reticulocyte count > 1.0 ULN -Platelets > 50 x 10^9/L -Neutrophils > 0.5 x 10^9/L -Vaccinated against *Neisseria meningitidis* types A,C,W,Y and B, *Streptococcus penumoniae*, and *Haemophilus influenzae* Type B Key Exclusion Criteria: -Active bacterial infection -Hereditary complement deficiency -History of bone marrow transplantation -MI, stroke, or cardiac arrythmias	ITT: 1. 41 2. 39 PP: 1. 38 2. 39 Attrition: 1. 3 (7%) 2. 0 (0%)	Primary Endpoint: Adjusted LSM change in Hgb level from baseline to week 16, ITT population 1. 2.37 g/dL 2. -1.47 g/dL MD: 3.84 g/dL 95% CI: 2.33 to 5.34 P<0.001 Secondary Endpoints: 1.Proportion of ITT population that did not require a transfusion (NI assessment) 1. 35 (85%) 2. 6 (15%) Adjusted Difference: 62.5% 95% CI 48.3 to 76.8 P<0.0001 NI met: Yes (NIM -20%) 2.LSM change from baseline in absolute reticulocyte count in ITT population (NI assessment) 1. -135.8 x 10^9 cells/L 2. 27.8 x 10^9 cells/L Difference: -163.6 x 10^9 cells/L 95% CI -189.9 to -137.3 P<0.0001 NI met: Yes (NIM 10) 3. LSM change in LDH level, ITT population (NI assessment) 1. -14.8 U/L 2. -10.1 U/L Difference: -4.63 95% CI -181.3 to 172.04 P=0.96 NI met: No (NIM 20) 4. LSM score on FACIT-F scale in ITT population 1. 9.2 points 2. -2.65 points	NA NA NA NA	Serious Adverse Events 1. 7 (17%) 2. 5 (13%) Total Adverse Events 1. 36 (88%) 2. 34 (87%) Infections 1. 12 (29%) 2. 10 (26%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to pegcetacoplan or eculizumab via IRT for 16 week randomization phase. Randomization stratified according to number of PRBC transfusions during 12 months prior to study enrollment (< 4 or ≥ 4) and platelet count at screening (<100,000 or ≥100,000 x 10^{9}cells/L. Baseline characteristics were balanced between groups. Performance Bias: High. Open label study design. Patients and investigators were not blinded to treatment arm. Detection Bias: High. Open label study design as dosing frequency and route of administration was different between the 2 treatment arms. Attrition Bias: Low. None of the eculizumab-treated patients withdrew from the study. 7% (n=3) of pegcetacoplan patients withdrew from the study due to breakthrough hemolysis. Reporting Bias: Unclear. Protocol available online. All outcomes reported as specified. Only the ITT NI analysis was reported. PP analysis not reported in supplemental appendix. Other Bias: Unclear. Trial designed by Apellis Pharmaceuticals. Sponsor responsible for trial oversight and data analysis. **Applicability**: Patient: Adults with PNH who have continued to have anemia despite treatment with eculizumab. Cannot apply data from this study to patients that are treatment naïve. Intervention: Pegcetacoplan dosing based on safety observed in Phase 2 trials. Comparator: Eculizumab has proven efficacy in PNH patients and is an appropriate active comparator. Outcomes: Changes in hemoglobin reflect extent of anemia due to hemolysis in PNH patients. Setting: 44 centers in Australia, Belgium, Canada, France, Germany, Japan, South Korea, Russia, Spain, United Kingdom, and US. Approximately 18% of study centers were in the US.

				Difference: 11.9 95% CI 5.49 to 18.25 NI not assessed	NA			

Abbreviations: AC = active comparator; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; dL = deciliter; FACIT-F scale = Functional Assessment of Chronic Illness Therapy-Fatigue; Hgb = hemoglobin; IRT = interactive response technology; ITT = intention to treat; IV = intravenous; L = liter; LDH = lactate dehydrogenase; LSM = least squares mean; MC = multi-center; MD = mean difference; MI = myocardial infarction; mo = months; N = number of subjects; NA = not applicable; NI = noninferiority; NIM = noninferiority margin; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PNH = postural nocturnal hemoglobinuria; PP = per protocol; PRBC = packed red blood cells; RCT = randomized clinical trial; SC = subcutaneous; y = years; U = units; ULN = upper limits of normal; US = United States

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Appendix 1: Current Preferred Drug List

Biologics for Rare Conditions

Generic	Brand	Route	Form	PDL
ravulizumab-cwvz	ULTOMIRIS	INTRAVEN	VIAL	Y
inebilizumab-cdon	UPLIZNA	INTRAVEN	VIAL	Y
satralizumab-mwge	ENSPRYNG	SUB-Q	SYRINGE	Y
eculizumab	SOLIRIS	INTRAVEN	VIAL	N
Medications highlighted in grey are indicated for PNH within this drug class.				

Uncategorized Medication

Generic	Brand	Route	Form	PDL
pegcetacoplan	EMPAVELI	SQ	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 20, 2021

1. *exp Hemoglobinuria, Paroxysmal/* *1829*
2. *eculizumab.mp.* *1674*
3. *ravulizumab.mp.* *48*
4. *complement C3/or pegcetacoplan.mp* *4795*
5. *2 or 3 or 4* *6377*
6. *1 and 5* *381*
7. *limit 6 to (english language and humans)* *329*
8. *limit 7 to (clinical study or 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 protocol or clinical trial or controlled clinical trial or guideline or meta-analysis or randomized controlled trial or "systematic review")* *5*

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

EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use
Initial U.S. Approval: 20XX

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA
See full prescribing information for complete boxed warning.

Meningococcal infections may occur in patients treated with EMPAVELI and may become rapidly life-threatening or fatal if not recognized and treated early. Use of EMPAVELI may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B. (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. (5.1)**
- **Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of EMPAVELI unless the risks of delaying EMPAVELI therapy outweigh the risks of developing a serious infection. See *Warnings and Precautions (5.1)* for additional guidance on managing the risk of serious infections.**
- **Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected. (5.1)**

EMPAVELI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the EMPAVELI REMS, prescribers must enroll in the program. (5.2)

----------INDICATIONS AND USAGE----------
EMPAVELI is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1)

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

- Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.3)

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

- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
EMPAVELI is contraindicated in:

- Patients with hypersensitivity to pegcetacoplan or any of the excipients. (4)
- Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism. (4, 5.1)
- Patients with unresolved serious infection caused by encapsulated bacteria. (4)

---------- WARNINGS AND PRECAUTIONS ----------
Use caution when administering EMPAVELI to patients with:

- Serious infections caused by encapsulated bacteria. (5.1)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed. (5.3)
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT). (5.5)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions in patients with PNH (incidence ≥10%) were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2021

Eculizumab (Soliris®)

Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is approved by the FDA for the following indications:
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
  - Treatment of generalized myasthenia gravis (MG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive

Length of Authorization:

Up to 12 months

Requires PA:

- Soliris® (eculizumab) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies? Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis one of the following: • Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), OR • atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #6	**No:** Go to #7
6. Does the requested dosing align with the FDA- approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for a diagnosis of myasthenia gravis in an adult patient who is ACh Receptor (AChR) antibody-positive?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Has the patient tried: • at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR • at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab[1]

	Eculizumab (Soliris®)
FDA-approved Indications	• Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody • Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) • Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive

Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
Recommended aHUS dose in patients less than 18 yo	**Body Weight**	**Induction Dose**	**Maintenance Dose**
	5 kg to 9 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300mg every 3 weeks
	10 kg to 19 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300mg every 2 weeks
	20 kg to 29 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600mg every 2 weeks
	30 kg to 39 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
	≥ 40 kg	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended generalized MG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. Soliris (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 4/21 (DM)
Implementation: 5/1/21

Ravulizumab (Ultomiris®)

Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Ravulizumab is approved by the FDA for the following indications:
  - The treatment of adults and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS)

Length of Authorization:

Up to 12 months

Requires PA:

- Ultomiris® (Ravulizumab) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 4
4. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for ~~meningococcal~~ vaccination in patients with complement deficiencies? Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
~~4.~~5. Is the diagnosis for a patient at least 1 month of age or older with atypical Hemolytic Uremic Syndrome (aHUS) or Paroxysmal Nocturnal Hemoglobinuria (PNH) ? Note: Ravulizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~5.~~6. Does the requested dosing align with the FDA-approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Intravenous Infusion Dosing for Ravulizumab[1]

Body Weight	Loading Dose	Maintenance Dose (begins 2 weeks after loading dose)
5 to 9 kg	600 mg	300 mg every 4 weeks
10 to 19 kg	600 mg	600 mg every 4 weeks
20 to 29 kg	900 mg	2,100 mg every 8 weeks
30 to 39 kg	1,200 mg	2,700 mg every 8 weeks
40 to 59 kg	2,400 mg	3,000 mg every 8 weeks
60 to 99 kg	2,700 mg	3,300 mg every 8 weeks
100 kg or greater	3,000 mg	3,600 mg every 8 weeks

1. Ultomiris™ (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 6/2021.

P&T/DUR Review: 12/21 (DM); 4/21 (DM)
Implementation: TBD; 5/1/21

Pegcetacoplan (Empaveli™)

Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Pegcetacoplan is approved by the FDA for the following indication:
  - Treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH)

Length of Authorization:

Up to 12 months

Requires PA:

- Empaveli™ (pegcetacoplan) 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 the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 4

Approval Criteria		
4. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2 week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis for an adult (age 18 years or older) with Paroxysmal Nocturnal Hemoglobinuria (PNH)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/21 (DM)
Implementation: TBD

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Drugs for Endometriosis and Uterine Fibroids

Date of Review: December 2021

Date of Last Review: March 2019 (Endometriosis); Nov 2019 (Elagolix); Jan 2019 (Hormone replacement); May 2015 (GnRH Agonists)

Dates of Literature Search: 01/01/2019 – 09/01/2021

Generic Name: Relugolix**,** Estradiol, and Norethindrone acetate

Brand Name (Manufacturer): MYFEMBREE (Myovant Sciences)

Dossier Received: Yes

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

Purpose for Class Update:
This drug class update examines recently published comparative evidence for safety and efficacy of oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists, danazol, and GnRH antagonists for management of moderate to severe pain due to endometriosis. In addition, evidence supporting FDA approval for relugolix, estradiol, and norethindrone combination therapy for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal populations will be evaluated.

Research Questions:
1. What is the comparative evidence assessing safety and efficacy of drug therapies for the treatment of moderate to severe pain associated with endometriosis?
2. What is the efficacy of relugolix, estradiol, and norethindrone combination therapy compared to placebo or currently available therapy for the management of heavy menstrual bleeding associated with uterine fibroids?
3. Is relugolix, estradiol, and norethindrone combination therapy safe for the management of heavy menstrual bleeding associated with uterine fibroids?
4. Are there any subgroups (based on age, race, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with oral contraceptives, progestins, GnRH agonists, danazol, or GnRH antagonists for endometriosis or uterine fibroids?

Conclusions:
- No new evidence focused on safety and efficacy of pharmacologic agents used to manage pain associated with endometriosis has been published since the last Pharmacy and Therapeutics Committee review in 2019.
- A 2017 systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) evaluated evidence supporting the safety and efficacy of different treatment strategies for management of uterine fibroids.[1] Gonadotropin-releasing hormone agonists (leuprolide and goserelin) and progesterone

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receptor agents (mifepristone and ulipristal) reduced fibroid size and improved fibroid-related symptoms, including bleeding and quality of life (moderate strength of evidence except quality of life for GnRH agonists; low strength of evidence).[1] Mifepristone is only FDA-approved for one-time use as emergency contraception.[2] Ulipristal acetate is approved outside the US, but post-marketing reports of rare but serious liver injury, including need for liver transplantation, have prompted the European Medicines Agency and other regulatory agencies to significantly limit the use of daily ulipristal acetate for uterine fibroid treatment.[3] Few well-designed trials directly compare different treatment options.[1]

- A 2020 Cochrane review evaluated the effectiveness of progestin or progestin-releasing intrauterine systems in treating premenopausal women with uterine fibroids.[4] Because of low-quality evidence, it is not clear if the levonorgestrel-releasing intrauterine device (IUD) reduces abnormal uterine bleeding, reduces the size uterine fibroids or increases hemoglobin levels in premenopausal women with uterine fibroids, compared to oral contraceptives.[4] There is insufficient evidence to determine whether oral progestins reduce abnormal uterine bleeding as effectively as the GnRH agonist, goserelin acetate, but women reported fewer adverse events, such as hot flashes with oral progestins.[4]
- A 2018 Cochrane meta-analysis assessed the safety and effectiveness of antifibrinolytic medications (tranexamic acid) as a treatment for heavy menstrual bleeding.[5] The evidence was low to moderate quality: the main limitations were risk of bias (associated with lack of blinding, and poor reporting of study methods), imprecision and inconsistency.[5] When compared to placebo, antifibrinolytics were associated with reduced mean blood loss in women with heavy menstrual bleeding (mean difference [MD] -53.20 mL per cycle, 95% confidence interval [CI] -62.70 to -43.70; I^2= 8%; 4 RCTs, participants = 565; moderate-quality evidence).[5] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has traditionally been defined as greater than 80 mL blood loss per cycle.[6] There was no clear evidence of a difference between antifibrinolytics and placebo in adverse events (RR 1.05, 95% CI 0.93 to 1.18; 1 RCT, participants = 297; low-quality evidence).[5]
- The National Institute for Health and Care Excellence (NICE) issued guidance in 2018 for assessment and management of heavy menstrual bleeding.[7] Off-label use of the levonorgestrel-releasing IUD is recommended as first line therapy for women with fibroids less than 3 cm diameter which are not causing distortion of the uterine cavity.[7] If a woman with heavy menstrual bleeding declines the levonorgestrel-releasing IUD or is not a suitable candidate , the following off-label pharmacologic treatments can be considered: tranexamic acid, combined hormonal contraception, or cyclic oral progestins.[7] If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for endometrial ablation, hysterectomy or myomectomy.[7] Surgical pretreatment with a GnRH agonist should be considered if uterine fibroids are causing an enlarged or distorted uterus.[7]
- An oral fixed-dose combination of the GnRH receptor antagonist relugolix, estradiol, and norethindrone acetate (MYFEMBREE), was approved by the FDA for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women May 2021.[8] Food and Drug Administration (FDA) approval of the combination relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg once daily formulation was based on the results of 2 identically designed, 24-week, randomized, double-blind, phase 3 trials (LIBERTY-1 and LIBERTY-2).[9]
- In both LIBERTY trials, significantly more women responded to relugolix combination therapy and achieved the primary endpoint of menstrual blood loss of less than 80 mL and a 50% or greater reduction from baseline in menstrual blood loss over the final 35 days of treatment compared to women who received placebo.[9] Moderate quality evidence demonstrated 73% of the participants in the relugolix combination therapy group in LIBERTY-1 were responders versus 19% in the placebo group (difference 55%; 95% CI 44 to 65; p<0.001; number needed to treat [NNT] 2).[9] Similar results were observed in LIBERTY-2 as 71% of relugolix combination-treated participants were responders, versus 15% in the placebo-treated group (difference 56%; 95% CI 46 to 66; p<0.001; NNT 2).[9]
- The most common adverse reactions observed with relugolix administration (incidence ≥3%) were hot flush, hyperhidrosis or night sweats, hypertension, abnormal uterine bleeding, alopecia, and decreased libido.[8] Because the combination relugolix product contains estrogen and progestin, the prescribing information contains a black boxed warning regarding the risk of thromboembolic disorders and vascular events.[8] Relugolix, estradiol, and norethindrone acetate combination therapy is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased

risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.[8] In addition, the use of relugolix therapy should be limited to 24 months due to the risk of bone loss which may not be reversible and it is contraindicated in women with known osteoporosis.[8]

- There is insufficient long term comparative efficacy and safety data for relugolix, estradiol and norethindrone therapy. More information is needed regarding the long-term benefits and risks of relugolix therapy. No trials are available that directly compare relugolix the other FDA-approved treatments for fibroid-associated heavy menstrual bleeding (i.e., elagolix, leuprolide).
- There is insufficient evidence to determine if certain subpopulations would benefit from specific therapies approved for management of fibroid-associated bleeding or pain associated with endometriosis.

Recommendations:

- Implement new prior authorization (PA) criteria for GnRH modifiers to evaluate GnRH antagonists, including include relugolix, estradiol, and norethindrone combination therapy, separately from GnRH agonists (e.g., leuprolide).
- Review comparative costs of therapy in executive session.

Summary of Prior Reviews and Current Policy

The GnRH modulators were last reviewed at the March 2019 Pharmacy and Therapeutics (P & T) meeting. Prior authorization criteria for GnRH agonists and antagonists were combined into one document entitled GnRH modifiers (**Appendix 5**). Additional PA revisions were approved by the P & T Committee to ensure safe and appropriate utilization of GRH modifiers:

- Revise step therapy for elagolix to remove requirement for trial of acetaminophen or a nonsteroidal anti-inflammatory agent prior to trial of elagolix
- Limit PA approval to the FDA recommended duration of therapy for elagolix to minimize bone loss
- Add endometriosis diagnosis with step therapy for leuprolide, goserelin, and nafarelin
- Reinforce warnings about bone mineral density loss with use of GnRH modifiers

Between January 2020 and January 2021 there approximately 500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of uterine fibroid-related diagnosis and approximately 300 women with a diagnosis of endometriosis. **Appendix 1** lists the GnRH modulators on the Preferred Drug List (PDL). All of the GnRH modifiers are non-preferred and require PA. In the second quarter of 2021, 1 claim was processed in the FFS population for leuprolide.

Background:

Uterine Fibroids

Uterine fibroids (i.e., leiomyomas) are benign smooth muscle tumors of that arise primarily in 3 regions of the uterus (submucosal, intramural, and subserosal) in women of reproductive age.[10] In the United States (US), an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[11] Uterine fibroids account for nearly 30% of all hysterectomies among American women ages 18–44 years.[11] Factors that are associated with an increased risk of uterine fibroids include premenopausal status, family history, nulliparity, hypertension, and obesity.[12] On average, Black women are younger at onset of fibroids, and have larger and more numerous tumors, and are more likely to be anemic and have surgical interventions for fibroids.[11] These observed differences are likely due to inequities in social determinants of health as well as implicit and explicit bias among the medical community.[13] Experiences of racism can delay women from seeking care for uterine fibroid symptoms until they are severe, and bias in medicine at the systemic and individual levels may affect the quality of diagnosis and treatment they receive.[13] In addition, differences in social determinants of health such as limitations on access to quality education, jobs, stable housing, safe neighborhoods, nutritious foods, and health insurance are associated with inequitable uterine fibroid treatment among Black women.[14,15] Racial disparities in

treatment, such as higher rates of hysterectomy and myomectomy (compared with nonsurgical therapy) and open hysterectomy (compared with minimally invasive approaches) have been reported among Black women compared with White women.[14] The prevalence of uterine fibroids does not appear to be higher among Latina and Asian women as compared with White women, but data are far more limited for these populations.[14]

Although they are often asymptomatic, uterine fibroids can cause excessive menstrual bleeding, pelvic pain, and other symptoms that seriously affect a woman's quality of life.[11] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[6] Other fibroid symptoms include infertility, increased urinary frequency or incontinence, constipation, abdominal bloating, dyspareunia, and fatigue (due to anemia from heavy bleeding).[11] The evaluation of fibroids is based mainly on the patient's presenting symptoms: abnormal menstrual bleeding, bulk symptoms (i.e., abdominal protrusion, constipation or urinary frequency), pelvic pain, or findings suggestive of anemia.[10] Fibroids are sometimes found in asymptomatic women during routine pelvic examination or incidentally during imaging.[10] In the US, ultrasonography is the preferred initial imaging modality for fibroids.[10] Transvaginal ultrasonography is about 90% to 99% sensitive for detecting uterine fibroids, but it may miss subserosal or small fibroids.[10]

The alkaline hematin technique, which involves chemically measuring the blood content of used sanitary products, is considered the gold standard for menstrual blood loss determination and has traditionally been used to diagnose heavy menstrual bleeding.[16] The alkaline hematin method directly measures the volume of menstrual blood loss by comparing hematin from menstrual products against calibration curves created from a simultaneous venous blood sample.[17] The alkaline hematin laboratory testing of blood stained sanitary products has been utilized as a primary endpoint in a number of trials evaluating heavy menstrual bleeding with the levonorgestrel-releasing IUD, oral contraceptives, and leuprolide.[18] The FDA has found this test to be somewhat more objective than a pictorial bleeding assessment which directs the study participant to grade their volume of bleeding by comparing their sanitary products to pictures of sanitary products that have undergone some degree of saturation with known quantities of blood.[18]

Symptomatic fibroids may require medical or surgical intervention.[11] Surgical treatment includes hysterectomy, myomectomy, uterine artery embolization, and magnetic resonance–guided focused ultrasound surgery.[10] The 3 medications that have FDA-approval for managing fibroid-related bleeding are leuprolide acetate[19] and the 2 GnRH antagonists (i.e., elagolix and relugolix).[8,20] Several medications including oral contraceptives, levonorgestrel-releasing IUD, and tranexamic acid are used off-label to manage heavy menstrual bleeding associated with fibroids.

Slow release injectable leuprolide acetate received FDA approval in 1999 for preoperative management of patients with anemia caused by uterine fibroids.[21] Leuprolide for this indication is limited to 3 months of use. The recommended dosing regimens for uterine fibroids are 3.75 mg once a month for 3 months or a single 11.25 mg injection.[21] These regimens were found to increase hematocrit by 6% or more and hemoglobin by 2 g/dL or more in 77% of study participants at three months of therapy.[1] Although not listed as part of the indication, some clinicians found that the reduction in size of fibroids from leuprolide acetate treatment resulted in less surgical blood loss and less need for blood transfusions.[1] Other FDA-approved indications for leuprolide acetate include management of endometriosis-associated pain, palliative treatment of advanced prostatic cancer, and treatment of pediatric patients with central precocious puberty.[21,22]

Gonadotropin releasing hormone antagonists (i.e., elagolix and relugolix) are available as oral products and are formulated with low-dose hormonal add-back therapy to limit hypoestrogenic side effects. Elagolix received FDA-approval in 2018 for management of severe pain associated with endometriosis.[23] Elagolix causes a dose-dependent decrease in bone mineral density.[23] The extent of bone mineral density loss is greater with increasing duration of elagolix use and may not be completely reversible after discontinuing therapy.[23] For this reason, the duration of elagolix therapy is limited to 24 months in women without comorbidities.[23] For women with moderate hepatic impairment, the duration of elagolix therapy is limited to 6 months.[23] Evidence for the safety and efficacy of

elagolix in management of endometriosis-associated pain was presented at November 2019 P & T Committee meeting. Elagolix in combination with estradiol and norethindrone acetate (ORIAHNN), received FDA-approval in May 2020 for the treatment of fibroid-related heavy menstrual bleeding in premenopausal women for up to 24 months.[20] When the elagolix combination therapy is prescribed for fibroid-associated bleeding, it is dosed twice daily as 1 capsule of the fixed combination product in the morning and 1 capsule of elagolix 300 mg monotherapy in the evening.[20] This dosing regimen can be taken for up to 24 months.[20] More details about relugolix, the newest GnRH antagonist approved for management of fibroid-related bleeding, are discussed later in this class update.

According to NICE guidance, women with heavy menstrual bleeding associated with fibroids can start combined hormonal contraceptives containing estradiol and dienogest to reduce menstrual blood loss.[7] This is an off-label use of oral contraceptives. Levonorgestrel-releasing intrauterine devices have been found to decrease heavy menstrual bleeding in patients with and without uterine fibroids.[24] However, rates of IUD expulsion are higher in patients with uterine fibroids compared with patients without fibroids (11% versus 0 to 3%).[24] The risk of expulsion may be particularly increased in patients with uterine fibroids that distort the uterine cavity.[24] There is insufficient evidence to support the use of a levonorgestrel-IUD for the treatment of uterine fibroid symptoms other than bleeding.[4]

Tranexamic acid is an oral nonhormonal antifibrinolytic agent FDA-approved for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential.[25] Women who cannot or do not wish to take hormonal contraceptives may prefer this treatment. Tranexamic acid 1,300 mg three times a day can be taken for up to 5 days during monthly menstruation to reduce bleeding.[25] Due to the risk of thrombosis, tranexamic acid is contraindicated in patients at risk for thromboembolic disease or when used concomitantly with hormonal contraceptives.[25] Efficacy of tranexamic acid in women with fibroid-associated heavy menstrual bleeding has not been established.[24]

An AHRQ systematic review presented moderate strength of evidence that progesterone receptor modulators (i.e., mifepristone and ulipristal) reduce fibroid size and improve fibroid-related symptoms including bleeding and quality of life.[1] However, neither therapy is available in the US for management of fibroid-related symptoms. Mifepristone is only FDA-approved for one-time use as emergency contraception.[2] Ulipristal acetate is approved outside the US, but post-marketing reports of rare but serious liver injury, including need for liver transplantation, have prompted the European Medicines Agency and other regulatory agencies to significantly limit the use of daily ulipristal acetate for uterine fibroid treatment.[24]

Endometriosis

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[26] Although available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[26] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis. Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[27] Androgenic adverse effects, such as acne, hirsutism, and male pattern baldness, often limit the tolerability of danazol in women. Current first-line therapies to manage pain associated with endometriosis are oral contraceptives or progestin.[28] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[27,29] Most of the data supporting the use of oral contraceptives in managing endometriosis pain is observational and low-quality.[28]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy.[28] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[27] The FDA recommends the use of add-back hormonal therapy when a GnRH agonist is used for greater than 6 months.[28] Elagolix is the only GnRH antagonist approved to manage pain symptoms associated with endometriosis. Surgical management, including laparoscopy for definitive diagnosis, lysis of adhesions, and removal of visible implants, is an option in

women with endometriosis who do not respond to medical therapy, especially for those who are infertile.[27,29] Hysterectomy has also been recommended for women with severe, debilitating, and refractory endometriosis who do not wish to become pregnant and in whom other therapeutic measures have failed.[26]

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

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

Systematic Reviews:
Agency of Healthcare Research and Quality: Management of Uterine Fibroids
A 2017 AHRQ systematic review analyzed literature published from January 1985 to September 2016 to evaluate effectiveness and safety of interventions for management of uterine fibroids.[1] Significant outcomes included resolution of symptoms (pain and uterine bleeding) and reduction in the size of uterine fibroids. Patient-reported outcomes were frequently assessed and reported in 63% of studies.[1] Of the 43 RCTs reporting on effectiveness of medications, 10 studies had placebo or no treatment comparison groups.[1] Approximately one third of the RCTs were industry sponsored.[1] Women included in the studies were predominately premenopausal (39 studies).[1] Four RCTs were assessed as good quality, 12 as fair quality, and 27 as poor quality for effectiveness outcomes.[1]

Thirteen studies addressed the GnRH agonist, leuprolide, which included 7 studies of add-back hormonal therapy (2 good-quality RCTs, 2 fair-quality RCTs, and 9 poor-quality RCTs).[1] Three poor-quality studies evaluated goserelin.[1] Most RCTs ranged in sample size from 16 to 101 women.[1] This small study size limits power for discerning differences across treatment groups and virtually prohibits meaningful evaluation of factors that may influence outcomes within groups.[1] As in much of the fibroid literature, lack of follow-up over time is a limitation.[1] Most studies completed their follow-up of participants when treatment ended.[1] Only 7 studies followed women from 3 to 9 months after end of treatment, limiting the information about how durable the effects may be.[1] GnRH agonists reduced the size of fibroids, with reductions in volume of fibroids documented between 64 and 175 cm^3.[1] As a point of reference, the volume of a golf ball is 40 cm^3.[1] Six studies reported complete absence of bleeding during treatment with 3 trials noting statistical significance for clinically important reduction from baseline.[1] No study reported an increase in bleeding or worsening in hemoglobin or hematocrit.[1] Studies consistently reported significant improvement in measures of quality of life symptoms (days of bleeding, heavy menstrual bleeding, pelvic pressure, pelvic pain, urinary frequency, and constipation).[1] Harms associated with GnRH antagonists included onset of menopausal symptoms, unfavorable changes in lipid profile, declines in cognitive function and memory, and bone loss, although some of these can be ameliorated with hormonal add-back therapy.[1] In summary, moderate strength of evidence supports that GnRH agonists (with and without add-back hormonal therapy) reduce the size of fibroids and bleeding symptoms.[1] Low strength of evidence suggests that fibroid-related quality of life improves with and without add-back hormonal therapy.[1]

Seven studies provided data about outcomes after treatment with the anti-progestin, mifepristone.[1] All studies observed a decrease in the size of fibroids at the completion of the period of active treatment.[1] The magnitude of change in size of the largest fibroid ranged from a decrease of 37 cm^3 to 95 cm^3, with an

average decrease of 71 cm^3 among the 575 women receiving mifepristone.[1] All studies of mifepristone that assessed bleeding reported reduced bleeding.[1] Harms associated with mifepristone included spotting, elevations in liver function enzymes, and endometrial hyperplasia.[1] In summary, there is moderate strength of evidence that both mifepristone effectively reduced the size of fibroids and bleeding symptoms.[1] Of note, mifepristone is not FDA-approved for management of uterine fibroids.

The levonorgestrel-releasing IUD improved bleeding (the only outcome of interest reported); however, the single available trial was of poor quality including lack of participant masking.[1] Evidence was insufficient to assess the effectiveness of the levonorgestrel-releasing IUD on any outcomes.[1]

Six studies included agents that act at the estrogen receptor.[1] Three studies, 2 of fair quality and 1 of poor quality, investigated raloxifene (which acts as an anti-estrogen in breast and endometrial tissue) in comparison with placebo.[1] Fibroid size decreased by 4.4 cm^3 to 34.2 cm^3 in 2 studies of raloxifene and did not change size in another.[1] In raloxifene studies with premenopausal women, neither bleeding pattern (in 3 studies) nor hemoglobin levels (in 1 study) were improved compared with placebo.[1] A single poor quality study evaluated tamoxifen, which acts as an anti-estrogen within breast tissue and as an estrogen ligand in the endometrium.[1] Tamoxifen use in premenopausal women did not influence length or severity of bleeding compared with placebo.[1] Change in fibroid characteristics was not reported.[1] Two poor quality RCTs had a total of 42 women receiving hormone replacement therapy (transdermal estrogen replacement plus cyclic oral medroxyprogesterone acetate) after menopause.[1] They compared hormone therapy to tibolone (not available in United States) for menopausal symptom management with attention to whether treatment increased size of fibroids.[1] Growth was approximately 10 cm^3 , which is a quarter the size of a golf ball.[1] In summary, studies provide low strength of evidence that, if prescribed to women with fibroids for other conditions such as breast cancer prophylaxis, raloxifene will not cause significant growth of existing fibroids or exacerbate bleeding.[1] Evidence is insufficient to assess if tamoxifen or hormone replacement therapy does or does not promote fibroid growth.[1]

Uterine artery embolization (high strength of evidence) as well as high intensity focused ultrasound (low strength of evidence) are effective for decreasing fibroid size/volume.[1] High intensity focused ultrasound reduces fibroid size (low strength of evidence), but impact on quality of life was not measured.[1] Myomectomy and hysterectomy also improve quality of life (low strength of evidence).[30] Few well-designed trials directly compared different treatment options.[1] Evidence to guide choice of intervention is best when applied in the context of individual patient needs and preferences.[1]

Cochrane: Progestin Effectiveness in Uterine Fibroids

A 2020 Cochrane review evaluated the effectiveness of progestin or progestin-releasing intrauterine systems in treating premenopausal women with uterine fibroids. Literature was searched through July 2020 for the most recent update.[4] Four studies including 221 women with uterine fibroids met inclusion criteria.[4] The available evidence was low quality, downgraded for serious risk of bias, due to poor reporting of study methods, and serious imprecision.[4] At 12 months, low-quality evidence from 1 RCT in 44 women showed the levonorgestrel-releasing IUD reduced the percentage of abnormal uterine bleeding, measured with the alkaline hematin test (MD 77.50%, 95% CI 70.44 to 84.56); increased hemoglobin levels (MD 1.50 g/dL, 95% CI 0.85 to 2.15), or reduced fibroid size more than oral contraceptives (MD 1.90%, 95% CI -12.24 to 16.04).[4] The study did not measure adverse events.[4] Vasomotor symptoms (e.g. hot flashes) were only associated with goserelin acetate (55%), not with dienogest (1 RCT, 14 women; low-quality evidence) or with desogestrel (1 RCT, 16 women; low-quality evidence).[4] Because of low-quality evidence, it is not clear if the levonorgestrel-releasing IUD reduces abnormal uterine bleeding, reduces the size uterine fibroids or increases hemoglobin levels in premenopausal women with uterine fibroids, compared to oral contraceptives.[31] There is insufficient evidence to determine whether oral progestins reduce abnormal uterine bleeding as effectively as the GnRH agonist, goserelin acetate, but women reported fewer adverse events, such as hot flashes with progestins.[4]

Cochrane: Antifibrinolytics in Heavy Menstrual Bleeding

A 2018 Cochrane meta-analysis assessed the safety and effectiveness of antifibrinolytic medications (tranexamic acid) as a treatment for heavy menstrual bleeding.[5] The literature search was conducted through November 2017. The evidence was low to moderate quality: the main limitations were risk of bias (associated with lack of blinding, and poor reporting of study methods), imprecision and inconsistency.[5] When compared to placebo, antifibrinolytics were associated with reduced mean blood loss in women with heavy menstrual bleeding (MD -53.20 mL per cycle, 95% CI -62.70 to -43.70; I^2= 8%; 4 RCTs, participants = 565; moderate-quality evidence).[5] There was no clear evidence of a difference between antifibrinolytics and placebo in adverse events (RR 1.05, 95% CI 0.93 to 1.18; 1 RCT, participants = 297; low-quality evidence).[5] Only one thromboembolic event occurred in the two studies that reported this outcome.[5]

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[32-36]

New Guidelines

High Quality Guidelines:

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence issued guidance in 2018 for assessment and management of heavy menstrual bleeding due to various causes including fibroids.[7] Management of endometriosis is discussed under separate NICE guidance published in 2017.[37] At the time of publication, neither elagolix or relugolix had received approval for management of fibroid-associated bleeding. NICE guidance for use of these agents is expected in 2022. Heavy menstrual bleeding associated with fibroids should be managed as follows:

Off-label use of the levonorgestrel-releasing IUD is recommended as first line therapy for women with:[7]

- Fibroids less than 3 cm diameter which are not causing distortion of the uterine cavity
- No identified pathology

If a woman with heavy menstrual bleeding declines the levonorgestrel-releasing IUD or is not a suitable candidate the following off-label pharmacologic treatments can be considered:[7]

- Tranexamic acid
- Combined hormonal contraception
- Cyclic oral progestins

If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for:[7]

- Endometrial ablation
- Hysterectomy or myomectomy
- Pretreatment with a GnRH agonist should be considered if uterine fibroids are causing an enlarged or distorted uterus

Additional Guidelines for Clinical Context:

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists issued a practice bulletin focused on management of uterine fibroids in 2021.[24] Studies were reviewed and evaluated for quality using methods outlined by the US Preventative Services Task Force.[24] Literature published between January 2000 and July 2020 was reviewed for the recent update. However, the recommendations are not based on a systematic review. Stakeholder involvement, method of consensus, search terms, detailed search strategy and inclusion/exclusion criteria are not reported. When reliable research was not available, expert opinions from obstetrician–

gynecologists were used.[24] ACOG recommends medical treatments that reduce bleeding symptoms (levonorgestrel-releasing IUD, contraceptive steroids, tranexamic acid, and GnRH antagonists) or medications that reduce both bleeding and uterine fibroid size (GnRH agonists and selective progesterone receptor modulators) for management of fibroid-associated symptoms.[24] There is insufficient comparative evidence to guide recommendations on first-line medical therapy.[24] Treatment decisions should be guided by an individual patient's symptoms and treatment goals.[24] Medical management should be tailored to the size and location of fibroids, the patient's age, symptoms, desire to maintain fertility, and access to treatment.[24]

New Formulations or Indications:

- 5/1/2020: An extended release formulation of leuprolide acetate (FENSOLVI) received FDA-approval for treatment of pediatric patients 2 years of age and older with central precocious puberty.[19] The dose of this leuprolide formulation is 45 mg subcutaneously once every 6 months administered by a health care provider.[19] In contrast, the 7.5 mg, 11.25 mg, and 15 mg doses of leuprolide depot suspension (LUPRON DEPOT-PED) are administered intramuscularly every month, based on the child's weight, by a health care provider.[22] Two additional 11.25 mg and 30 mg LUPRON DEPOT-PED suspensions are designed to be administered every 3 months.[22]

  The efficacy of FENSOLVI was evaluated in an uncontrolled, open-label, single arm clinical trial in which 64 pediatric patients (62 females and 2 males, naive to previous GnRH agonist treatment) with central precocious puberty received at least one dose of FENSOLVI at a dosing interval of every 3 months and were observed for 12 months.[19] The mean age was 7.5 years (range 4 to 9 years) at the start of treatment. In pediatric patients with central precocious puberty, FENSOLVI reduced stimulated and basal gonadotropins to prepubertal levels.[19] Suppression of peak stimulated luteinizing hormone (LH) concentrations to 4 IU/L or less was achieved in 87% of pediatric patients by month 6 and in 86% of patients by month 12.[19] Suppression of estradiol or testosterone concentration to prepubertal levels at the 6-month assessment was achieved in 97% and 100% of patients, respectively.[19]

- 5/28/2020: A combination product of elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5mg (ORIAHNN) received FDA-approval for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.[20] A capsule containing elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5mg is taken in the morning and a capsule containing only elagolix 300 mg is taken in the evening.[20] The product is packaged in weekly blister packs to assist in adherence to the dosing regimen.

  The efficacy of ORIAHNN in the management of heavy menstrual bleeding associated with uterine fibroids was demonstrated in two randomized, double-blind, placebo-controlled studies (Study UF-1 and Study UF-2) in which 790 premenopausal women with heavy menstrual bleeding received elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg in the morning and elagolix 300 mg in the evening or placebo for 6 months.[38] Heavy menstrual bleeding at baseline was defined as having at least two menstrual cycles with greater than 80 mL of menstrual blood loss (MBL) as assessed by alkaline hematin method.[20] The primary endpoint in both studies was the proportion of responders, defined as women who achieved both 1) MBL volume less than 80 mL at the final month and 2) 50% or greater reduction in MBL volume from baseline to the final month.[20] Final month was defined as the last 28 days before and including the last treatment visit date or the last dose date. A higher proportion of elagolix-treated women were responders (68.5%) compared to placebo-treated women (8.7%) in study UF-1 (difference: 59.8%; 95% CI 51.1 to 68.5; $p<0.001$).[20] Similar results were observed in Study UF-2 (76.5% [elagolix] vs. 10.5% [placebo], difference: 66%; 95% CI 57.1 to 75.0; $p<0.001$).[20]

  The use of elagolix/estradiol/norethindrone should be limited to 24 months due to the risk of continued bone loss, which may not be reversible.[20] ORIAHNN carries a black boxed warning, similar to other combination estrogen/progestin products, regarding the increased risk of thromboembolic disorders especially in women at increased risk for these events including women over 35 years of age who smoke or women with uncontrolled hypertension.[20]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[39]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Leuprolide	ELIGARD, LUPRON	02/2019	Adverse Reactions: Postmarketing Experience Use In Specific Populations: Pregnancy	Adverse Reactions: Pituitary apoplexy-During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. Nervous System-Convulsions Respiratory System-Interstitial lung disease Pregnancy: Based on findings in animal studies and mechanism of action, leuprolide may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Expected hormonal changes that occur with leuprolide treatment increase the risk for pregnancy loss. In animal developmental and reproductive studies, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation in rats. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.
Leuprolide	ELIGARD, LUPRON	05/2017	Warnings and Precautions	Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Psychiatric events have been reported in patients taking GnRH agonists, including leuprolide acetate. Postmarketing reports with this class of drugs include symptoms of

				emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with LUPRON
Nafarelin	SYNAREL	05/2017	Warnings and Precautions	Post-marketing reports of convulsions have been observed in patients receiving GnRH agonists. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.
Histrelin	VANTAS	02/2019	Warnings and Precautions	Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.
Histrelin	VANTAS	12/2020	Warnings and Precautions	The safety and efficacy of histrelin have not been established in females. Based on findings from animal studies and its mechanism of action, histrelin can cause fetal harm when administered to a pregnant woman. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.

Randomized Controlled Trials:
A total of 24 citations were manually reviewed from the initial literature search. After further review, 24 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Relugolix/Estradiol/Norethindrone (MYFEMBREE)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

An oral fixed-dose combination of the GnRH receptor antagonist relugolix, estradiol, and norethindrone acetate (MYFEMBREE), was approved by the FDA for management of heavy menstrual bleeding associated with uterine fibroids in May 2021.[8] The recommended dose is 1 tablet containing relugolix 40mg, estradiol 1mg, and norethindrone acetate 0.5 mg once a day.[8] It is the second oral product to be FDA-approved for this indication. A combination product containing elagolix, estradiol and norethindrone acetate received FDA approval May 2020.[20] Relugolix was initially FDA-approved for treatment of adult patients with advanced prostate cancer in 2020 under the brand name ORGOVYX.[40] Relugolix, like elagolix, inhibits endogenous GnRH signaling by binding to GnRH receptors in the pituitary gland, suppressing release of LH and follicle stimulating hormone (FSH).[8] Suppression of LH and FSH results in decreased serum concentrations of estradiol and progesterone which curtail endometrial proliferation which in turn reduces menstrual bleeding.[8] Estradiol and norethindrone acetate are included in the fixed-dose combination tablet as hormonal add-back therapy. Estradiol reduces relugolix hypoestrogenic adverse effects, such as vasomotor symptoms and reductions in bone mineral density.[8] Norethindrone helps to prevent endometrial hyperplasia and malignancies associated with unopposed estrogen use.[8] Relugolix combination therapy is currently being investigated for management of endometriosis-associated pain and as an oral contraceptive.

Clinical Efficacy:

FDA approval of the combination relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg formulation was based on the results of 2 identically designed, 24-week, randomized, double-blind, phase 3 trials (LIBERTY-1 and LIBERTY-2).[9] The trials were conducted in a total of 770 premenopausal patients with fibroid-associated heavy menstrual bleeding.[9] Heavy menstrual bleeding was defined as a volume of menstrual blood loss of 80 mL or more per cycle for 2 cycles or a volume of 160 mL or more during 1 cycle.[9] Participants were randomly assigned in a 1:1:1 ratio to receive once-daily placebo, relugolix combination therapy (40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate) for 24 weeks, or delayed relugolix combination therapy (40 mg of relugolix monotherapy, followed by relugolix combination therapy, each for 12 weeks).[9] The delayed relugolix combination therapy regimen was added to the protocol to assess the benefit and safety of the addition of estradiol and norethindrone acetate on bone mineral density and vasomotor symptoms.[9] The primary efficacy end point in each trial was the percentage of participants with a response, defined as the volume of menstrual blood loss less than 80 mL and at least 50% reduction in volume from baseline, in the relugolix combination therapy group compared with the placebo group over 24 weeks.[9] Determination of blood loss was assessed using the alkaline hematin test. Key secondary end points were amenorrhea, volume of menstrual blood loss and anemia.

In both trials, significantly more women achieved menstrual blood loss of less than 80 mL and a 50% or greater reduction from baseline in menstrual blood loss over the final 35 days of treatment with relugolix combination therapy than with placebo.[9] A total of 73% of the participants in the relugolix combination therapy group in LIBERTY-1 were responders versus 19% in the placebo group (difference 55%; 95% CI 44 to 65; $p<0.001$; NNT 2).[9] Similar results were observed in LIBERTY-2 as 71% of relugolix combination-treated participants were responders, versus 15% in the placebo-treated group (difference 56%; 95% CI 46 to 66; $p<0.001$; NNT 2).[9] More participants in the delayed relugolix combination group also responded to therapy compared to placebo (80% in LIBERTY-1 and 73% in LIBERTY-2), but a statistical analysis was not completed.[9]

Compared with the placebo groups the relugolix combination therapy groups had significant improvements in key secondary end points, including amenorrhea, changes in volume of menstrual blood loss, and anemia assessment.[9] Amenorrhea over the last 35 days of the treatment period occurred in 52% and 50% of the participants receiving relugolix combination therapy in LIBERTY-1 and LIBERTY-2, respectively, as compared with 6% of those receiving placebo (difference 46%;

95% CI 37 to 56; P<0.001) and 3% of placebo-treated patients (difference 47%; 95% CI: 38 to 57; P<0.001), respectively.[9] The mean reduction in menstrual blood loss from baseline to week 24 in the relugolix combination therapy groups was 84% in both LIBERTY-1 and LIBERTY-2, as compared with 23% and 15%, respectively, in the placebo groups (P<0.001 for both comparisons).[9] Fifty percent or more of the participants who had anemia at baseline had an increase of more than 2 g/dL in hemoglobin levels with relugolix combination therapy, as compared with placebo.[9] Additional details about the LIBERTY-1 and LIBERTY-2 trials are described and evaluated below in **Table 5**.

Many patients with self-reported heavy menstrual bleeding and uterine fibroids did not pass screening owing to strict assessment criteria for LIBERTY-1 and LIBERTY-2, which could limit generalizability to the wider population of patients who might benefit from relugolix therapy. In addition, the duration of the trial was only 6 months. More information is needed regarding the long-term benefits and risks of relugolix therapy. No trials are available that directly compare relugolix the other FDA-approved treatments for fibroid-associated heavy menstrual bleeding (i.e., elagolix, leuprolide).

Clinical Safety:
The most common adverse reactions observed with relugolix combination therapy were hot flush, hyperhidrosis or night sweats, hypertension, abnormal uterine bleeding, alopecia, and decreased libido.[8] The frequency of these adverse events compared with placebo are presented in **Table 3.**

Table 3. Adverse Reactions Occurring in 3% or More of Women Treated with Relugolix/Estradiol/Norethindrone Acetate[8]

Adverse Reaction	Relugolix/Estradiol/Norethindrone N=254	Placebo N=256
Hot flush, hyperhidrosis, or night sweats	10.6%	6.6%
Hypertension	7.0%	0.8%
Abnormal uterine bleeding (includes menorrhagia, vaginal hemorrhage, polymenorrhea)	6.3%	1.2%
Alopecia	3.5%	0.8%
Decreased or loss of libido	3.1%	0.4%

Because the combination relugolix product contains estrogen and progestin, the prescribing information contains a black boxed warning regarding the risk of thromboembolic disorders and vascular events.[8] Estrogen and progestin combination products increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in persons at increased risk for these events.[8] Relugolix, estradiol, and norethindrone acetate combination therapy is contraindicated in persons with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including females over 35 years of age who smoke or have uncontrolled hypertension.[8]

The use of relugolix therapy should be limited to 24 months due to the risk of bone loss which may not be reversible and it is contraindicated in persons with known osteoporosis.[8] In LIBERTY-1 and LIBERTY-2 bone mineral density measured by dual-energy x-ray absorptiometry (DEXA) of the lumbar spine, total hip, and femoral neck was assessed at baseline, week 12 and week 24. In both trials, mean changes from baseline to week 24 in bone mineral density at the lumbar spine were not statistically significantly different between the relugolix combination group and the placebo group.[9] In LIBERTY 1 and LIBERTY 2, the mean percent difference from baseline at 12 weeks in bone mineral density at lumbar spine for relugolix combination therapy versus placebo was the -0.7 (95% CI −1.4 to 0.1) and -1.3 (95% CI -2.0 to -0.6), respectively.[9] In both trials the mean percent difference from baseline at 24 weeks in bone mineral density at lumbar spine

for relugolix combination therapy versus placebo was the same (difference −0.4%; 95% CI −1.2 to 0.3).[9] Similar results in LIBERTY 1 and LIBERTY 2 were observed in total hip bone mineral density assessments at 12 weeks between relugolix combination therapy and placebo (MD -0.4, ,95% CI -1.0 to 0.2 and MD -0.9, 95% CI -0.3 to 0.7, respectively).[9] The inclusion of the delayed relugolix combination therapy group in the LIBERTY trials allowed for the comparison of the effects of combination therapy with monotherapy.[9] In the delayed relugolix combination therapy group, the bone mineral density at the lumbar spine decreased from baseline at week 12 with relugolix monotherapy compared with placebo in LIBERTY-1 and LIBERTY-2 (difference -2.2; 95% CI -2.9 to -1.5 and difference -2.4; 95% CI -3.1 To -1.7, respectively).[9] Similar changes in lumbar spine bone density were observed at week 24 in LIBERTY-1 and LIBERTY-2 (difference -1.9, 95% CI -2.6 to -1.1 and difference -2.4, 95% CI -3.2 to -1.7, respectively).[9] Twelve weeks of monotherapy resulted in a loss of bone mineral density and a higher incidence of vasomotor adverse events, as compared with relugolix combination therapy, and although the transition to relugolix combination therapy prevented further loss of bone mineral density, it did not reverse the changes in bone mass.[9]

Other warnings and precautions associated with relugolix treatment include the risk of: depression, mood disorders, and suicidal ideation; hepatic impairment; elevated blood pressure; changes in menstrual bleeding pattern and reduced ability to recognize pregnancy; early pregnancy loss; and uterine prolapse or expuslsion.[8] Contraindications to relugolix, estradiol and norethindrone combination therapy include: current or history of breast cancer or other hormone-sensitive malignancies; known hepatic impairment or disease; and undiagnosed abnormal uterine bleeding.[8]

Relugolix is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 hepatic enzymes.[8] Concomitant use of an oral P-glycoprotein (P-gp) inhibitor increases serum concentrations of relugolix and is not recommended; if use of an oral P-gp inhibitor is necessary, relugolix should be taken at least 6 hours before the P-gp inhibitor.[8] Concurrent use of a combined P-gp and strong CYP3A inducer can reduce the efficacy of relugolix and should be avoided.[8]

Look-alike / Sound-alike Error Risk Potential: No results identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduced volume of menstrual blood loss (< 80 mL/month)
2) Improvement in anemia
3) Improved pain control
4) Quality of life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in volume of blood loss

Table 4. Pharmacology and Pharmacokinetic Properties[8]

Parameter	
Mechanism of Action	Relugolix is a gonadotropin-releasing hormone antagonist that decreases LH, FSH, estradiol and progesterone to reduce bleeding associated with fibroids.
Oral Bioavailability	62%
Distribution and Protein Binding	Protein binding, albumin 68% to 71%

Elimination	Renal excretion: 4.1%, fecal excretion: 81%
Half-Life	61.5 hours
Metabolism	Extensive hepatic metabolism: substrate of CYP3A, CYP2C8, and P-gp

Abbreviations: FSH = follicle stimulating hormone; LH = luteinizing hormone; P-gp = P-glycoprotein

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.Al-Hendy A, et al[9] LIBERTY-1 DB, MC, PC, phase 3 RCT	1. Placebo once day x 24 weeks 2. Relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethindrone 0.5 mg) x 24 weeks 3. Delayed relugolix combination therapy: relugolix 40mg monotherapy x 12 weeks followed by relugolix combination therapy x 12 weeks	Demographics: 1. Mean age: 42 y 2. Percent ≥ 40 y: 70% 3. Ethnicity: White: 45% Black: 49% Other: 6% 4. Median BMI: 30 kg/m^2 5.Median MBL: 190 mL Key Inclusion Criteria: 1. Premenopausal women 18 to 50 years of age 2. Diagnosis of fibroids confirmed by ultrasound 3. Heavy menstrual bleeding with a volume ≥ 160 mL in 1 cycle or ≥ 80 mL in 2 cycles 4. Regular menses with <14 days duration cycling between 21 to 38 days for at least 3 months prior to screening	ITT: 1. 127 2. 128 3. 132 PP: 1. 105 2. 100 3. 103 Attrition: 1. 22 (17%) 2. 28 (22%) 3. 29 (22%)	Primary Endpoint: Percent of responders defined as: 1) Volume of menstrual blood loss <80 mL and 2) Reduction of ≥ 50% from baseline in volume of MBL over last 35 days of treatment 1. 19% (n=24) 2. 73% (n=93) Difference: 54% 95% CI: 44 to 65 P<0.001 Secondary Endpoints: Achieved amenorrhea over last 35 days of treatment: 1. 6% (n=7) 2. 52% (n=67) Difference: 46% 95% CI: 37 to 56 P<0.001 Percent change from baseline to Week 24 in MBL volume 1. -23% 2. -84% Difference: -61% 95% CI: -74 to -49 Proportion of women with hemoglobin level ≤ 10.5 g/dL	54/2 46/3 NA	Adverse Events: 1. 66% 2. 62% 3. 73% Serious Adverse Events: 1. 2% 2. 5% 3. 2% Adverse Event Leading to Discontinuation: 1. 4% 2. 5% 3. 12% Hot Flashes 1. 8% 2. 11% 3. 36% Hypertension 1. 0% 2. 5% 3. 2% 95% CI and p-values NR for all outcomes		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 1:1:1 via interactive website. Baseline demographics well balanced between treatment arms. Subjects stratified by mean volume of MBL (< 225 mL vs ≥ 225 mL) and geographic region (North America v. the rest of the world). Performance Bias: Unclear. Placebo tablets and capsules packaged in blister cards similar to active comparators. Method of investigator blinding to treatment not described. Detection Bias: Unclear. Method of outcome assessor blinding not described. Subjects kept electronic diaries to report bleeding and product use, which is subject to recall bias. Attrition Bias: High. Over 20% of subjects in both active comparator arms withdrew due to adverse effects, lack of efficacy, loss to follow up or protocol deviation. Reporting Bias: Low. Protocol available on line. All pre-specified outcomes reported. Other Bias: Unclear. Manufacturer designed trial and analyzed data. **Applicability**: Patient: Stringent exclusion criteria may have limited participation for women who would benefit from therapy. Well diversified based on race. Intervention: Relugolix 40 mg once daily was effective in reducing MBL in Phase 2 trial. Comparator: Placebo is an appropriate comparator, but comparison with a similar

		Key Exclusion Criteria: 1. Bone mineral density z score less than -2.0 (osteoporosis) 2. HMB due to ovarian polyps, cysts, or other gynecological disorders 4. Any surgical procedure for fibroids 6 months prior to screening 5. History metabolic disease (i.e., hyperparathyroidism, hyperthyroidism, anorexia) 6. History of bisphosphonate, teriparatide, denosumab, or calcitonin therapy used to treat bone mineral density loss 7. Breast cancer 8. Thromboembolic disease		at baseline who achieved an increase > 2 g/dL at week 24 1. 22% (n=5/23) 2. 50% (n=15/30) Difference: 28% 95% CI: 4 to 43	NA			agent such as elagolix would have provided meaningful head-to-head data. Outcomes: Proportion of responders using volume of MBL has been used in previous clinical trials evaluating efficacy of other medications used to reduce HMB associated with fibroids. Setting: 80 sites in Africa, Europe, North America and South America. Number of sites by country: United States n=63 Brazil n=3 Italy n=5 Poland n=5 South Africa n=3 United Kingdom n=1
2. Al-Hendy A, et al[9] LIBERTY-2 DB, MC, PC, phase 3 RCT	1. Placebo once day x 24 weeks 2. Relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethindrone 0.5 mg) x 24 weeks 3. Delayed relugolix combination therapy: relugolix 40mg monotherapy x 12 weeks	Demographics: 1.Mean age: 42 yo 2. Percent ≥ 40 yo: 70% 3. White: 41% Black: 53% Other: 6% 4.Median BMI: 31 kg/m^2 5.Median MBL: 185 ml Key Inclusion Criteria: see LIBERTY-1	ITT: 1. 129 2. 125 3. 127 PP: 1. 102 2. 102 3. 98 Attrition: 1. 27 (21%) 2. 23 (18%) 3. 29 (23%)	Co-Primary Endpoints: Percent of responders defined as: 1)Volume of menstrual blood loss <80 mL and 2)Reduction of at least 50% from baseline in volume of MBL over last 35 days of treatment 1. 15% (n=19) 2. 71% (n=89) Difference: 56% 95% CI: 46 to 66 P<0.001 Secondary Endpoints:	56/2	Adverse Events: 1. 59% 2. 60% 3. 71% Serious Adverse Events: 1. 3% 2. 1% 3. 2% Adverse Event Leading to Discontinuation: 1. 5% 2. 2%		**Risk of Bias (low/high/unclear)**: Selection Bias: see LIBERTY-1 Performance Bias: see LIBERTY-1 Detection Bias: see LIBERTY-1 Attrition Bias: High. Over 20% of subjects in placebo and 1 active comparator arm withdrew due to adverse effects, lack of efficacy, loss to follow up or protocol deviation. Reporting Bias: Low. Protocol available on line. All pre-specified outcomes reported. Other Bias: see LIBERTY-1 **Applicability**: Patient: see LIBERTY-1 Intervention: see LIBERTY-1

	followed by relugolix combination therapy x 12 weeks	Key Exclusion Criteria: see LIBERTY- 1		Achieved amenorrhea over the last 35 days of treatment 1. 3% (n=4) 2. 50% (n=63) Difference: 47% 95% CI: 38 to 57 P<0.001 Percent change from baseline to Week 24 in mean MBL volume 1. -15% 2.- 84% Difference: -69% 95% CI: -84 to -54 Proportion of women with hemoglobin level ≤ 10.5 g/dL at baseline who achieved an increase > 2 g/dL at week 24 1. 5% (n=2/37) 2. 61% (n=19/31) Difference: 56% 95% CI: 37 to 75	47/3 NA NA	3. 11% Hot Flashes 1. 4% 2. 6% 3. 35% Hypertension 1. 3% 2. 4% 3. 6% 95% CI and p-values NR for all outcomes		Comparator: see LIBERTY-1 Outcomes: see LIBERTY-1 Setting: 99 sites in Africa, Europe, North America and South America. Number of sites by country: United States n=67 Belgium n=4 Brazil n=4 Chile n=4 Czech Republic n=4 Hungary n=7 Poland n=5 South Africa n=4

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; DB = double blind; CI = confidence interval; dL = deciliter; HMB = heavy menstrual bleeding; ITT = intention to treat; kg = kilogram; m = meter; MBL = menstrual blood loss; MC = multi-center; mg = milligram; ml = milliliters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo control; PP = per protocol; RCT = randomized clinical trial; yo = years old

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23. ORLISSA (elagolix) oral tablets. Prescribing Information. North Chicago, IL; AbbVie, Inc. February 2021.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix/estradiol/norethindrone	ORIAHNN	ORAL	CAP SEQ	N
goserelin acetate	ZOLADEX	SUB-Q	IMPLANT	N
histrelin acetate	SUPPRELIN LA	IMPLANT	KIT	N
histrelin acetate	VANTAS	IMPLANT	KIT	N
histrelin acetate	SUPPRELIN	SUB-Q	KIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	KIT	N
leuprolide acetate	LUPRON DEPOT	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT (LUPANETA)	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LEUPROLIDE ACETATE	SUB-Q	KIT	N
leuprolide acetate	ELIGARD	SUB-Q	SYRINGE	N
leuprolide acetate	FENSOLVI	SUB-Q	SYRINGE	N
leuprolide acetate	LEUPROLIDE ACETATE	SUB-Q	VIAL	N
leuprolide/norethindrone acetate	LUPANETA PACK	MISCELL	KT SYR TAB	N
nafarelin acetate	SYNAREL	NASAL	SPRAY	N
triptorelin pamoate	TRELSTAR	INTRAMUSC	VIAL	N
triptorelin pamoate	TRIPTODUR	INTRAMUSC	VIAL	N
relugolix/estradiol/norethindrone	MYFEMBREE	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to August 30, 2021

1. Exp ENDOMETRIOSIS/	15420
2. Exp GOSERELIN/	1081
3. Exp LEUPROLIDE/	2161
4. NAFARELIN/	129
5. Elagolix.mp.	80
6. Exp MEDROXYPROGESTERONE ACETATE/	3184
7. NORETHINDRONE/	1119
8. DANAZOL/	878
9. relugolix.mp.	35
10. exp Leiomyoma	12741
11. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	8090
12. 1 or 10	27701
13. 11 and 12	886

14. limit 13 to (english language and humans and (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 consensus development conference or controlled clinical trial or equivalence trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 24

Appendix 3: Prescribing Information Highlights

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

MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS
See full prescribing information for complete boxed warning

- **Estrogen and progestin combinations, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, especially in women at increased risk for these events. (5.1)**
- **MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension. (4)**

INDICATIONS AND USAGE

MYFEMBREE is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. (1)

Limitations of Use
Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible. (1, 5.2, 6)

DOSAGE AND ADMINISTRATION

- Exclude pregnancy and discontinue hormonal contraceptives prior to MYFEMBREE initiation. (2.1)
- Take one tablet orally once daily. (2.2)
- Take the missed dose of MYFEMBREE as soon as possible the same day and then resume regular dosing the next day at the usual time. (2.3)
- If concomitant use of oral P-gp inhibitors is unavoidable, take MYFEMBREE at least 6 hours before taking the P-gp inhibitor. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: fixed-dose combination containing relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg (3)

CONTRAINDICATIONS

- High risk of arterial, venous thrombotic, or thromboembolic disorder. (4)
- Pregnancy. (4)
- Known osteoporosis. (4)
- Current or history of breast cancer or other hormone-sensitive malignancies. (4)
- Known hepatic impairment or disease. (4)
- Undiagnosed abnormal uterine bleeding. (4)
- Known hypersensitivity to components of MYFEMBREE. (4)

WARNINGS AND PRECAUTIONS

- Thromboembolic Disorders and Vascular Events: Discontinue MYFEMBREE if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Discontinue MYFEMBREE if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. (5.1)
- Bone Loss: Decreases in bone mineral density (BMD) that may not be completely reversible. Baseline and periodic BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss. (5.2)
- Depression, Mood Disorders, and Suicidal Ideation: Advise patients to seek medical attention for new onset or worsening depression, anxiety, or other mood changes. (5.4)
- Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury. (5.5)
- Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop MYFEMBREE if blood pressure rises significantly. (5.7)
- Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing MYFEMBREE. MYFEMBREE may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue MYFEMBREE if pregnancy is confirmed. (5.8)
- Risk of Early Pregnancy Loss: Can cause early pregnancy loss. Advise women to use effective non-hormonal contraception. (5.9)
- Uterine Fibroid Prolapse or Expulsion: Advise patients to seek medical attention for severe uterine bleeding. (5.10)
- Hypersensitivity Reactions: Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs. (5.14)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 3%) are hot flush, hyperhidrosis or night sweats, uterine bleeding, alopecia, and decreased libido. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Myovant Sciences, Inc. at 1-833-MYOVANT (1-833-696-8268) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid use of MYFEMBREE with oral P-gp inhibitors. (7.1)
- Avoid use with combined P-gp and strong CYP3A inducers, as the exposure of the components of MYFEMBREE may be decreased. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed while taking MYFEMBREE. (8.2)

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

Revised: 05/2021

Appendix 4: Key Inclusion Criteria

Population	Premenopausal women with uterine fibroids
Intervention	Relugolix/estradiol/norethindrone
Comparator	Placebo
Outcomes	Reduced volume of menstrual blood loss
Timing	6 months
Setting	Outpatient

Gonadotropin-Releasing Hormone Agonists

Goal(s):

- Restrict pediatric use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan (e.g., central precocious puberty or gender dysphoria)
- Promote use that is consistent with medical evidence and product labeling

Length of Authorization:

- Up to 6 months

Requires PA:

- GnRH agonists prescribed for pediatric patients less than 18 years of age
- Non-preferred products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the prescriber a pediatric endocrinologist?	**Yes:** Go to #4	**No:** Go to #8
4. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code. Record age and gender assigned at birth	
5. Is the diagnosis central precocious puberty (ICD10 E30.1, E30.8) or other endocrine disorder (E34.9)?	**Yes:** Approve for up to 6 months	**No:** Go to #6

Approval Criteria		
6. Is the diagnosis gender dysphoria (ICD10 F64.2, F64.1)?	**Yes:** Go to #7	**No:** Go to #12
7. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.* *From Guideline Note 127: To qualify for cross-sex hormone therapy, the patient must: A) have persistent, well-documented gender dysphoria B) have the capacity to make a fully informed decision and to give consent for treatment C) have any significant medical or mental health concerns reasonably well controlled D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness
8. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #9
9. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	**Yes:** Approve for up to 3 months	**No:** Go to # 10
10. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Approve for 6 months. *Note maximum recommended duration of therapy for nafarelin, leuprolide, and goserelin is 6 months. If requesting continuation of therapy beyond 6 months, pass to RPh. Deny; medical appropriateness.	**No:** Pass to RPh. Deny; medical appropriateness *First-line therapy options such as hormonal contraceptives or progestins do not require PA
12. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.		

P&T / DUR Review: *12/21 (DM); 3/19 (DM); 5/15*
Implementation: *TBD; 5/1/19*

Gonadotropin-Releasing Hormone Antagonists

Goal(s):

- Promote safe use of elagolix in women with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months
- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

Requires PA:

- Elagolix
- Elagolix/estradiol/norethindrone
- Relugolix/estradiol/norethindrone

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Is this request for management of moderate to severe pain associated with endometriosis in a patient ≥18 years of age?	**Yes**: Go to #6	**No:** Go to #11

Approval Criteria		
6. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as combined hormonal contraceptives or progestins do not require PA
7. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors? (e.g. cyclosporine, gemfibrozil, etc.)?	**Yes:** Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #10	**No:** Approve for 6 months * FDA approved dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
10. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months * FDA approved dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

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

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

Implementation: TBD; 5/1/19

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Drug Class Update with New Drug Evaluation: Growth Hormones

Date of Review: December 2021

Date of Last Review: June 2021 (updated PA criteria and FDA indications); September 2017 (literature scan)
Dates of Literature Search: 10/01/2017 - 09/14/2021

Generic Name: lonapegsomatropin-tcgd

Brand Name (Manufacturer): Skytrofa (Ascendis Pharma, Inc.)
Dossier Received: no

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

Research Questions:
1. Is there new comparative evidence that growth hormone (GH) agents differ in efficacy or effectiveness in pediatric patients with growth hormone deficiency or related funded conditions?
2. Is there any new comparative evidence that GH agents differ in harms?
3. Are there specific subpopulations for which one GH agent is better tolerated or more effective than other available agents?
4. What is the evidence for efficacy and harms for the new GH agent, lonapegsomatropin, recently approved to treat pediatric patients with growth failure due to inadequate secretion of endogenous GH?

Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., GH) products and formulations.
- There is no new evidence to support that one GH agent is better tolerated or more effective than other available agents for specific subpopulations.
- The Food and Drug Administration (FDA) approval of lonapegsomatropin was based on efficacy data from one Phase 3 clinical trial (heiGHt; study 301) of 161 patients with growth hormone deficiency (GHD).[1-4] The FDA-approved indication is for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous GH.[2-5]
- The heiGHt trial (study 301) reported that once weekly lonapegsomatropin for 52 weeks was non-inferior to daily somatropin as demonstrated by a 11.2 cm/year annualized height velocity compared to 10.3 cm/year, respectively[Estimated treatment difference (ETD) 0.9 cm/year (95% CI 0.2 to 1.5; p=0.009)[1-5] Although statistical significance for non-inferiority was demonstrated, the ETD of 0.9 cm/yr was relatively small and was >50% smaller in magnitude than the non-inferiority margin (2 cm/yr), therefore it is unclear whether this statistical difference is clinically meaningful.
- The safety of lonapegsomatropin in pediatric patients with GHD was primarily evaluated based on data from the pivotal active-controlled phase 3 trial (study-301). There were no serious adverse events (SAEs) observed. The most common adverse events associated with lonapegsomatropin treatment and

≥4% more frequently than daily somatropin included pyrexia (15%), viral infection (15%), cough (11%), nausea/vomiting (11%), arthralgia/arthritis (7%), and hemorrhage (7%).[1-5]

- There is insufficient evidence to assess long-term safety of lonapegsomatropin beyond one year or once adult height, as determined by bone age, is achieved.[2]
- With the studied population primarily pediatric (mean age of 8.5 years), male (82%), and white (94%), it is unclear whether lonapegsomatropin would demonstrate similar safety and efficacy in subpopulations of different ages, gender, race or ethnic backgrounds represented in Oregon Medicaid.[1-5]

Recommendations:

- Maintain lonapegsomatropin as non-preferred in the Growth Hormone PDL class.
- Update prior authorization (PA) criteria for GH agents to include lonapegsomatropin.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

- In June 2021, prior authorization criteria for the Growth Hormone PDL class was updated to align fee-for-service PA criteria with the latest Health Evidence Review Commission (HERC) guidance for use of GH and its FDA-approved indications.
- Somapacitan-beco was added to Growth Hormone PDL class and made non-preferred.
- Treatment for adult human growth hormone deficiency is currently not listed as a funded condition on the prioritized list of health services.

Background:

Growth Hormone (GH) influences many of the metabolic processes performed by somatic cells and triggers protein synthesis in a wide range of bodily tissues.[6-8] The anterior pituitary secretes GH in short busts at different times throughout the night and daily following meals, after exercise, and during stress.[6-8] GH increases growth in children by its direct action on growth plates and indirectly stimulates cell proliferation by production of various growth factors such as insulin-like growth factor-1 (IGF-1) in the liver and peripheral tissues.[6-8] Although prenatal growth is not dependent upon GH, its indirect effects on IGF-1 production is crucial for prenatal and postnatal development, especially in a child's first year of life.[6-8] GH also reduces the utilization of glucose in peripheral tissues and stimulates lipolysis as well as growth of skeletal muscle and cartilage.[6-8] Hypoglycemia, hypothyroidism, and/or defective primary or secondary sexual development may be other signs of pituitary dysfunction which can be a result of hormone deficiencies such as adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), or gonadotropin.[6-8] There are a variety of disorders in which endogenous growth hormone production is inadequate to meet the developmental demands required for specification, organization, and maturation of somatotropic cells.[6-8]

There are several pediatric conditions where growth may be severely compromised. Early GH therapy has been used to improve height velocity and normalize childhood growth in children with growth hormone deficiency (GHD).[9-12] GHD is a result of pituitary gland dysfunction that occurs in roughly 1:4000 – 10000 live births.[7] Overall, the clinical manifestations of GHD vary among individual patients, and the diagnostic process is a complex, multistep process involving clinical history, physical examination with detailed growth pattern assessment, biochemical testing, and pituitary imaging.[9-12] GHD is the most common endocrine cause of short stature, which is defined as a height 2 standard deviations below the average for age, sex, and race. GHD may be isolated or may exist with other pituitary hormone deficiencies.[9-12] Pediatric patients with absolute GHD typically present with normal birth weight, then begin to show early growth failure at 6-12 months followed by notable decreases in growth velocity until 3 years of age.[6-8] Patients with GHD may also display signs such as delayed bone age, jaundice, central obesity, and craniofacial abnormalities.[6-8, 10] Congenital GHD is rare and is typically caused as a result of genetic mutation or structural brain

malformations.[8-12] Acquired GHD may occur in either child- or adulthood secondary to pituitary or hypothalamic tumors, head injury, central nervous system (CNS) infection, or due to other conditions which lead to an insufficient production of GH.[7-10] Some medications, such as glucocorticoids and stimulants, may result in transient GH deficiency and short stature.[6-11] Besides short stature, GHD leads to risk of hypoglycemia due to the patients' high sensitivity to insulin and loss of counter-regulatory mechanisms.[6-11] **Table 1** outlines GH Research Society consensus guidelines for times to consider immediate investigation into GHD.[9-11]

Table 1: Considerations for immediate investigation of potential GHD[9-11]

Height: ▪ 3 SD below mean for age (severe short stature) ▪ 2 SD below mean for age and height velocity > 1 SD below mean for chronological age over past year or decrease in height SD > 0.5 over past year in children > 2 years old ▪ > 1.5 SD below mid-parental height
Height Velocity: ▪ > 2 SD below mean over past year or > 1.5 SD below mean over past 2 years
Signs of intracranial lesion
Signs of multiple pituitary hormone deficiency
Neonatal signs of GHD

GHD=growth hormone deficiency; SD=standard deviations

Growth failure in children may be the result of isolated GHD, but compromised growth may also be present in those with chronic illness, genetic syndromes, or skeletal disorders.[11 9] Recombinant GH (rGH) is a first-line agent for GHD and is also approved for treatment of many other pediatric conditions that affect growth (**Table 2**).[8,9] Somatropin is the standard rGH preparation and is typically administered daily by subcutaneous injection.[8-12] When appropriate, rGH is generally initiated at an early age due to a more robust growth response and therapy is continued until growth has ceased.[9-12]

Table 2: FDA-approved Uses for Recombinant Growth Hormone

Condition	Etiology/Pathology	Clinical Manifestations	rGH Function	Approved rGH Preparation	Population Indication
GHD[6,7]	Impaired production of GH from congenital malformations/genetic defects or acquired causes (e.g. trauma, infection, malignancy)	Early growth failure at 6-12 months with decreased growth velocity until 3 years of age, delayed bone age, jaundice, central obesity, craniofacial abnormalities, hypoglycemia, hypothyroidism, defective primary or secondary sexual development	In children, used to normalize adult height and avoid extreme shortness in children and adolescents with GHD. In adults, decreased visceral fat and	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Saizen™ Zomacton™ Skytrofa™ Sogroya™	Pediatric; Adult Pediatric Adult

			increased muscle mass, and increased exercise capacity		
PWS[13]	Deletions or unexpressed regions of paternal chromosome 15 (15q11-13) leads to generalized hypothalamic insufficiency	Short stature, mental retardation, hyperphagia with obesity, and hyperflexibility	Foster linear growth, improve muscle mass, enhance satiety and reduce weight gain	Genotropin™ Norditropin™ Omnitrope™	Pediatric
Noonan Syndrome[14]	Mutation in the RAS-MAPK signaling pathway which disrupts numerous hormones, cytokines, and growth factors that control cell proliferation, migration, differentiation, and survival	Face dysmorphology, short stature, congenital heart defect (e.g. pulmonary valve stenosis, hypertrophic cardiomyopathy), and developmental delays	Correction of short stature and improve growth	Norditropin™	Pediatric
Turner Syndrome[15]	Complete, partial absence, or structural abnormality of 1 X chromosome (45,X) in phenotypic female	Lymphedema, excess skin folds on neck, failure to thrive, slow growth, amenorrhea, and infertility	Improve short-term growth and increase final height; prevent short stature (females <4 years old)	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Zomacton™	Pediatric
Idiopathic Short Stature[10]	Unknown	Low to normal height velocity (< 5 cm/year from age 5 years until puberty), height below midparental centile range (height > 2 standard deviations below population mean for age and gender)	Increase short-term height velocity, and may increase final height in children	Genotropin™ Humatrope™ Norditropin™ Nutropin AQ™ Omnitrope™ Zomacton™	Pediatric
SHOX Deficiency[16]	Missing gene that encodes transcription factor expressed for developing skeletal	Short stature, skeletal dysplasia and severe limb deformity	Appears to increase height velocity and linear growth in prepubertal children	Humatrope™ Zomactron™	Pediatric

	tissue for long-bone growth				
CKD with Growth Failure[17]	Reduced GFR leading to growth retardation	Reduced height velocity and stunted growth	Reported to improve growth during the first year of administration	Nutropin AQ™	Pediatric
Small Gestational Age [9]	Maternal/placental or genetic factors that result in a fetus or newborn infant whose weight and/or crown-heel length is less than (2 SD below mean) expected for their gestational age and sex	Persistent short stature; Higher mortality rate due to cardiovascular disease	To accelerate linear growth, improve body composition, blood pressure, and lipid metabolism	Genotropin™ Humatrope™ Norditropin™ Omnitrope™ Zomacton™	Pediatric
HIV Associated Cachexia[18]	Altered metabolism and malabsorption due to HIV infection	Weight loss, anorexia, muscle atrophy, fatigue and weakness	To increase lean body mass, body weight and improve physical endurance	Serostim™	Pediatric, Adult
Short Bowel Syndrome[19]	Reduction of functional intestinal surface area from intestinal resection or tissue damage leads to malabsorption of nutrients, fluid, and/or electrolytes.	Diarrhea, dehydration, electrolyte abnormalities, weight loss, confusion and apathy	To increase weight, lean/fat-free body mass, and nutritional absorption	Zorbtive™	Adult

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GFR = glomerular filtration rate; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; PWS= Prader-Willi syndrome; rGH = recombinant growth hormone; SHOX = Short stature homeobox-containing gene

Although most GH products are FDA approved to treat pediatric patients, not every GH formulation is identical.[20-28] For example, somatropin exists under 9 different brand names that are not always interchangeable.[20-28] Clinical practice guidelines do not distinguish among the various preparations of GH as there is limited evidence of differences in clinical outcomes from one brand to another.[9-12] Each formulation may have a different strength, administration device, and/or storage requirement.[20-28] Dosing frequency may also vary among different products and conditions.[20-28] The choice of preparation is individualized based on therapeutic needs, patient response, as well as adherence.[20-28] If more than one product is suitable, the most cost-effective product should be chosen.[12] GH is indicated for children who need GH therapy and who have open epiphyses.[9-12] Therapy is started at low doses then increased gradually to the minimum effective dose that results in normalized IGF-1 levels without major adverse effects.[8] The treatment of somatropin should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues, or

if final height is attained.[8-12] The decision to stop treatment should be made in consultation with the patient and/or caregivers by a pediatrician with specialist expertise in managing growth hormone disorders in children or an adult endocrinologist.[12]

Adult GHD (AGHD) is most often due to hypopituitarism secondary to head trauma, tumor of the hypothalamus or pituitary gland, or the consequences of cancer treatment such as surgery or radiation.[30-31] Growth hormone deficiency is characterized by decreased lean body mass and bone mineral density, increased visceral adiposity, abnormal lipid profile, decreased muscle strength and decreased exercise endurance.[30-31] The diagnosis of GH deficiency is confirmed if other pituitary hormones such as thyroid stimulating hormone (TSH), corticotropin (ACTH), and gonadotropins are also diminished.[30-31] A subnormal serum insulin-like growth factor-1 (IGF-1) concentration or subnormal serum GH response to a stimulation test also assists in confirming AGHD.[30-31] The insulin tolerance test (ITT) and GHRH-arginine test are two tests recommended by the Endocrine Society to establish diagnosis of AGHD.[30-31] However, GH stimulation testing is invasive, time consuming, and can have increased risks in patients with seizure disorders or cardiovascular disease.[30-31]

The Health Evidence Review Commission (HERC) guidance currently restricts use of GH to funded diagnoses where there is medical evidence of effectiveness and safety.[32] HERC guidance continues to specify that treatment with GH for children with conditions such as gonadal dysfunction, panhypopituitarism, iatrogenic and other pituitary disorders should only continue until adult height, as determined by bone age, is achieved.[32] There are only 3 conditions for which GH therapy is FDA approved for use in adults: cachexia associated with AIDS (Serostim®)[26], short bowel syndrome (Zorbtive®)[28] and GH deficiency.[20-25,29] HIV associated with cachexia and short bowel syndrome are OHP-covered conditions for adults by their respective FDA-approved GH agents.[32] However, treatment for adult human growth hormone deficiency is currently not a funded condition on the HERC prioritized list of health services.[32]

During 2020 in the OHP FFS population, the most common indications identified based on medical claims for GHD-related diagnosis included short stature in children and hypopituitarism. Patients with diagnoses for other conditions such as Turner's syndrome, Prader-Willi syndrome, and other congenital malformations associated with short stature were relatively infrequent. There were 28 patients with claims for growth hormone agents in quarter 2 of 2021, which represents a moderate expenditure to the Oregon Health Authority. Of these claims, 82% were for preferred therapies.

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

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

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

After review, 3 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high-quality practice guidelines were identified.

Additional Guidelines for Clinical Context:
In 2019, the American Association of Clinical Endocrinologists and American College of Endocrinology released guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the guidelines will not be reviewed in detail or relied upon for policy making decisions.[33]

After review, 2 guidelines were excluded due to poor quality or for lack of applicability to the OHP population.

New Formulations or Indications:
No new formulations or indications were identified since the last review.

New FDA Safety Alerts:
There were numerous safety alerts released by the FDA over the last 3 years regarding the use of various somatropin formulations. The main alerts are summarized in **Table 4**.

Table 4: Description of New FDA Safety Alerts[34]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Somatropin	Humatrope (H) Zomacton (Z) Norditropin (N)	10/2019 7/2018 2/2018	Warning	-Increased mortality in patients with acute critical Illness due to complications from open heart surgery, abdominal surgery, accidental trauma, or respiratory failure (H) -Cases of pancreatitis (especially children; females with Turner syndrome) (N,Z) -Increased risk of malignancy/neoplasms (H,Z) -Progression of preexisting scoliosis (N,H) -Patients with Turner syndrome have an increased risk of developing autoimmune thyroid disease and primary hypothyroidism (Z)

			Contraindication	-Acute critical illness after open heart surgery, trauma, etc due to increased mortality (N) -Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death (N) -Active malignancy (H)

Randomized Controlled Trials:
A total of 71 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** 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:
Lonapegsomatropin is a long-acting pegylated prodrug formulation of somatropin, or recombinant hGH, approved for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH).[2-5] Lonapegsomatropin is covalently bonded to a methoxypolyethylene glycol carrier via a TransCon linker, and is designed to be given once weekly subcutaneously via a specialized glass auto injector.[2-5] Lonapegsomatropin slowly releases hGH via hydrolysis and is deigned to maintain the same mode of action and distribution in the body as daily somatropin.[2-5] Upon release, hGH stimulates the GH-receptor in tissues and increases hepatic production of IGF-1 which leads to GH activity such as growth stimulation, increased lean body mass, and improved metabolic actions.[1-5] The FDA approved lonapegsomatropin based on study 310 ("heiGHt" trial), a pivotal phase 3, open-label, active controlled, parallel-group study of 162 patients with GHD.[1-5] The trial consisted of a screening period (up to 6 weeks plus up to 2 weeks between randomization and visit 1) and a treatment period (52 weeks of dosing with a total of 6 trial visits).[1-5] The patients were randomized 2:1 to either lonapegsomatropin (n=106) or Genotropin (n=56), respectively.[2-5] Study participants were primarily white (94%), male (82%), had a mean baseline height velocity of 3.9 cm/year, a height standard deviation score (SDS) of -3 and a mean age of 8.5 years.[2-5] Baseline demographics were overall similar between groups in all major areas and baseline characteristics of height velocity and height SDS also appeared evenly distributed.[2-5] Patients with prior exposure to GH or IGF-1 therapies; a history of malignancy, evidence of malnourishment, idiopathic short stature, small for gestational age, or other non-GHD related causes of short stature were excluded.[1-4] The primary endpoint was annualized height velocity (AHV; cm/year) after 52 weeks based on a wall-mounted, calibrated stadiometer.[1-5] The AHV calculation used was AHV = (change in height [cm] ÷ change in time[days]) x 365 days.[1-4] The pre-specified non-inferiority margin was 2 cm/year, and the investigators planned a test for superiority if non-inferiority was achieved.[1-5] Secondary end points included AHV, height SDS, numerous IGF-1 lab measurements, and bone age assessed at predefined timepoints over 52 weeks.[1-5] Lonapegsomatropin 0.24 mg/kg was administered once weekly subcutaneously in 105 patients while 56 patients received once daily somatropin 0.034 mg hGH/kg.[1-5] The FDA also evaluated safety data from 2 other Phase 3 studies with pediatric GHD: CT-302 which was a 26-week, multi-site, open-label, uncontrolled trial with 146 patients from 24 international sites and CT-301EXT,

an ongoing, long term open-label, uncontrolled extension trial which enrolled 296 patients at 63 international sites.[2-4] There were no endpoints specified for study CT-302 or CT-301EXT.[2-4]

Patients treated with once weekly lonapegsomatropin for 52 weeks achieved 11.2 cm/year annualized height velocity while patients treated with once daily somatropin achieved an annualized height velocity of 10.3 cm/year which was considered statistically significant using the sponsor's pre-specified ANCOVA method (Estimated treatment difference (ETD) 0.9 cm/year; 95% CI 0.2 to 1.5; p=0.009).[1-5] With the upper boundary of the 95% CI less than the non-inferiority margin of 2, non-inferiority was attained.[1-4] Based on the pre-specified analysis, statistical superiority was also achieved as the lower limit of the two-sided CI of the treatment difference greater than or equal to 0 cm/year..[1-4] Lonapegsomatropin also demonstrated a relatively small but statistically significant change in Height SDS compared to placebo (1.10 vs. 0.96, respectively; ETD 0.14 (95% CI, 0.03 to 0.26; p=0.015).[1-5] The data used by the study sponsor to calculate Height SDS changes were from an ANCOVA model that included baseline age, peak GH levels (log transformed) at stimulation test and baseline height SDS as covariates, and treatment and sex as factors.[1-4]

This trial had some inherent limitations. Because lonapegsomatropin was administered once weekly compared to Genotropin given once daily, neither patients nor investigators were blinded to treatment. Due to the controlled nature of the study, it is unknown whether a once-weekly formulation would increase or decrease adherence compared to daily dosing if patients were to self-administer. Although statistical significance for non-inferiority was demonstrated, the treatment difference (0.9 cm/yr) between lonapegsomatropin and Genotropin was relatively small and was >50% smaller in magnitude than the non-inferiority margin (2 cm/yr). It is unclear whether this statistical difference is clinically meaningful. The lower boundary margin was set at >0, therefore statistical superiority was established. However, since the rationale for non-inferiority margin was not described it is unclear whether there was sufficient evidence available to warrant statistical (and clinical) superiority versus the standard of care.

Clinical Safety:
The safety population included 305 patients from 3 studies who had received at least one dose of lonapegsomatropin.[2-5] In study 301, adverse events related to treatment occurred in 12 patients (11%) in the lonapegsomatropin group compared to 10 patients (18%) in the Genotropin arm.[2-5] There were no serious adverse events (SAEs) observed that were related to treatment.[2-5] There were 3 treatment emergent adverse events (TEAEs) overall, 2 in the lonapegsomatropin group (lipoatrophy, urticaria) and one in the Genotropin arm (injection site-related swelling) that led to a dose reduction. No TEAEs resulted in drug discontinuation or death.[2-5] In the single-arm CT-302 safety study, there was one SAE and 4% of patients experienced a TEAE related to the study drug. There were no treatment discontinuations due to adverse events in the lonapegsomatropin group.[2-5] The most common adverse events associated with treatment included pyrexia, hemorrhage, viral infection, arthralgia/arthritis, cough, nausea and vomiting (see **Table 5**).[2-5]

Table 5. Adverse Reactions Occurring in ≥5% Lonapegsomatropin-Treated Patients and ≥4% More Frequently than in Somatropin-Treated Patients. [2,5]

	Lonapegsomatropin-tcgd (N=105) n (%)	Genotropin (N=56) n (%)
Pyrexia	16 (15%)	5 (9%)
Infection, viral	16 (15%)	6 (11%)
Cough	11 (11%)	4 (7%)
Nausea and vomiting	11 (11%)	4 (7%)
Hemorrhage	7 (7%)	1 (2%)
Arthralgia and arthritis	6 (7%)	1 (2%)

Adverse events of special interest (AESI) included on the FDA label included injections site reactions, increased risk of neoplasms, glucose intolerance, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses, progression of pre-existing scoliosis, pancreatitis, and lipoatrophy.[2,5] The AESI listed on the label are consistent with the known hGH class specific side effects and not limited to lonapegsomatropin.[2-5] Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. [2, 5] Lonapegsomatropin is contraindicated in patients with acute critical illness, active malignancies and with hypersensitivity to the drug.[5] FDA labeling has also limited the indication of lonapegsomatropin to patients 1 year or older with a body weight >11.5 kg due to the lowest available dosage strength available in that formulation.[5]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Final height
2) Growth/height velocity
3) Health-related quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Annualized height velocity (AHV; cm/year) after 52 weeks

Table 6: Pharmacology and Pharmacokinetic Properties.[2,3]

Parameter	
Mechanism of Action	A long-acting, pegylated prodrug of a human growth hormone (somatropin) that binds to the GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and numerous pharmacodynamic effects on tissues and metabolic processes.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd=0.13 L/kg; Protein binding not available
Elimination	3.2 mL/hour/kg
Half-Life	30.7 hours
Metabolism	Protein catabolism in both liver and kidneys

Abbreviations: GH=growth hormone; kg=kilogram; ml=milliliters; Vd=volume of distribution

Table 7: Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Thornton, et al. [1] 2021 Phase 3, OL, R, AC, PG	1. Lonapegsomatropin 0.24 mg hGH/kg/wk 2. Genotropin (somatropin) 0.034 mg hGH/kg/ day	Demographics: 1. Mean age: 8.5 years 2. Mean height: 112.7 cm 3. Mean bone age: 5.9 years 4. Mean height velocity: 3.9 cm/yr 5. Mean height SDS: -3 6. Male: 82% 7. Ethnic group: White (94.4%) Key Inclusion Criteria: -Prepubertal Tanner stage 1, GH therapy naïve -Boys: 3-12 yrs; Girls 3-11 yrs -Height SDS ≤ -2, standardized for chronological age/sex or height SDS less than 1.5 below the mid-parental height -BMI within ±2 SD of mean BMI for chronological age and sex -Confirmed GHD by 2 different GH stimulation tests. -Bone age 6 months less than chronological age -Baseline IGF-1 SDS ≤ -1, standardized for age and sex -Normal fundoscopy at screening Key Exclusion Criteria: -Children with a body weight<12kg -Tanner stage >1 -Prior exposure to recombinant hGH or IGF-1 therapy -Children w/ past or present intracranial tumor growth or malignancy -Children born small for gestational age, with idiopathic short stature, with psychosocial dwarfism, or other causes of short stature -Children with malnutrition	ITT: 1. 105 2. 56 Attrition: 1. 2 (2%) 2. 0 (0%)	Primary Endpoint: AHV (cm/yr) at Week 52 1. 11.2 2. 10.3 ARD=0.9 (95% CI, 0.2 to 1.5) p-value=0.009 Secondary Endpoints: Change in height SDS at 52 weeks 1. 1.10 2. 0.96 ARD=0.14 (95% CI, 0.03 to 0.26); P = 0.01)	N/A for all	No serious adverse effects reported at 52 weeks TEAEs 1. 2/105 (2%) 2. 1/56 (2%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Subjects were centrally randomized in a 2:1 ratio but no details on methods. Baseline demographics similar in both treatment groups. Performance Bias: (High) Open label study due to inability to conceal once weekly versus daily formulation and lack of double-dummy use. Doses could be adjusted at the discretion of the investigator after discussion with the medical monitor due to symptoms or lab results. Detection Bias: (Unclear) Bone age was read by a blinded central bone age reader and auxology performed by the same blinded auxologist at each visit when possible. Method of blinding was not reported. Attrition Bias: (Low) Similar rates of study withdrawal in both arms with similar reasons for discontinuation. Reporting Bias: (Unclear) Study protocol not available. Not all secondary outcomes reported (e.g. IGFBP-3 and IGFBP-3 SDS values) Other Bias: (Unclear) Sponsored by the manufacturer Ascendis Pharma, who directly employed or provided financial support to several authors through grants or personal fees. One primary author is an advisory board consultant for the manufacturer. **Applicability**: Patient: Appropriate diagnostic criteria were used, including evaluation of bone age, height at baseline; subjects underwent testing with 2 different GH stimulation tests in order to confirm the GHD diagnosis. However, exclusion of diabetics (A1c ≥8%) and inclusion of mostly males and white race may limit applicability to females and other racial or ethnic subgroups in the OHP population. Intervention: Fixed doses of rhGH were used Subjects started at a dose of 0.24 mg hGH/kg/week; starting dose consistent with

		-Any clinically significant abnormality likely to affect growth or the ability to evaluate growth -Poorly controlled DM, defined as hemoglobin A1c ≥ 8% or diabetic complications -chromosomal abnormalities -Closed epiphyses						recommended initial rhGH dose of 0.16-0.24 mg/kg/week Comparator: Genotropin (somatropin) appropriate standard of care and dosed reasonably at 0.034 mg hGH/kg/day Outcomes: AHV is a surrogate endpoint that has been accepted by the FDA for the approval of several other rhGH products for treatment of pediatric subjects with growth failure due to GHD Setting: 54 sites including Armenia, Australia, Belarus, Bulgaria, Georgia, Greece, Italy, New Zealand, Poland, Romania, Russia, Turkey, Ukraine, United States

Abbreviations: AC=active comparator; AHV=annualized height velocity; ARD=absolute risk difference; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; GH=growth hormone; GHD=growth hormone deficiency; (r)hGh=(recombinant)human growth hormone; IGF-1=insulin-like growth factor-1; ITT = intention to treat; kg=kilogram; mITT = modified intention to treat; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL=open label; PG=parallel group; PP = per protocol; R=randomized; SD = standard deviation; SDS=standard deviation score

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Appendix 1: Current Preferred Drug List

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

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to September 14, 2021>

1	somapacitan.mp.	15
2	somatropin.mp.	279
3	somatotropin.mp.	8163
4	humatrope.mp.	27
5	nutropin.mp.	25
6	serostim.mp.	39
7	zomacton.mp.	5
8	saizen.mp.	38
9	norditropin.mp.	91
10	zorbtive.mp.	3
11	genotropin.mp.	117
12	omnitrope.mp.	54
13	growth hormone.mp. or Growth Hormone/	75581
14	human growth hormone.mp. or Human Growth Hormone/	19768
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14/	76289
16	limit 15 to (full text and humans and yr="2018 -Current" and (clinical trial, all or controlled clinical trial or meta analysis or "systematic review"))	71

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SKYTROFA™ (lonapegsomatropin-tcgd) for injection, for subcutaneous use

Initial U.S. Approval: 2021

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

SKYTROFA is a human growth hormone indicated for the treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH) (1).

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

SKYTROFA should be administered subcutaneously into the abdomen, buttock, or thigh with regular rotation of the injection sites (2.5).
The recommended dose is 0.24 mg/kg body weight once-weekly.

See Full Prescribing Information for instructions on preparation and administration of drug (2.4, 2.5).

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

SKYTROFA is a lyophilized powder available in single-dose, dual-chamber, prefilled cartridges containing lonapegsomatropin-tcgd and diluent, Water for Injection, as follows:
For injection: 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg and 13.3 mg (3).

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

- Acute critical illness (4)
- Hypersensitivity to somatropin or any of the excipients in SKYTROFA (4)
- Children with closed epiphyses (4)
- Active malignancy (4)
- Active proliferative or severe non-proliferative diabetic retinopathy (4)
- Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment due to risk of sudden death (4)

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

- Severe Hypersensitivity: Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention (5.2).
- Increased Risk of Neoplasms: Monitor patients with preexisting tumors for progressions or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with somatropin – in particular meningiomas in patients treated with radiation to the head for their first neoplasm (5.3).
- Glucose Intolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycemic drugs in diabetics may require adjustment (5.4).
- Intracranial Hypertension: Exclude preexisting papilledema. May develop and is usually reversible after discontinuation or dose reduction (5.5).
- Fluid Retention (i.e., edema, arthralgia, carpal tunnel syndrome): May occur. Reduce dose as necessary (5.6).
- Hypoadrenalism: Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (5.7).
- Hypothyroidism: May first become evident or worsen (5.8).
- Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or persistent hip/knee pain (5.9).
- Progression of Preexisting Scoliosis: May develop (5.10).
- Pancreatitis: Consider pancreatitis in patients with persistent severe abdominal pain (5.11).

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

Most common adverse reactions (≥5%) in pediatric patients include: viral infection, pyrexia, cough, nausea and vomiting, hemorrhage, diarrhea, abdominal pain, and arthralgia and arthritis (6).

To report SUSPECTED ADVERSE REACTIONS, contact Ascendis Pharma, Inc., at 1-844-442-7236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Replacement Glucocorticoid Treatment: Patients treated with glucocorticoid for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of SKYTROFA (7).
- Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment: Adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatment to avoid both hypoadrenalism and an inhibitory effect on growth (7).
- Cytochrome P450-Metabolized Drugs: SKYTROFA may alter the clearance. Monitor carefully if used with SKYTROFA (7).
- Oral Estrogen: Larger doses of SKYTROFA may be required (7).
- Insulin and/or Other Antihyperglycemic Agents: Dose adjustment of insulin or antihyperglycemic agent may be required (7).

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

Revised: 8/2021

Appendix 4: Key Inclusion Criteria

Population	Children and adolescents with GHD or GHD-related diagnosis
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Final height, growth/height velocity, health-related quality of life
Timing	Weeks to years
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Growth Hormones

Goal(s):

- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with GH in children should continue only until adult height, as determined by bone age, is achieved. Treatment is not included for isolated deficiency of human growth hormone in adults.

Length of Authorization:

- Up to 12 months

Requires PA:

- All GH products require prior authorization for OHP coverage. Treatment of human growth hormone deficiency for adults is not funded by the OHP.

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/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the request for an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the agent being prescribed by, or in consultation with, a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient an adult (>18 years of age)?	**Yes:** Go to #10	**No:** Go to #6
6. Is the diagnosis funded?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #8
8. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
10. Is the request for the treatment of isolated human growth hormone deficiency in an adult (E23.0) or short stature due to an endocrine disorder (E34.3), or another unfunded condition? Per Guideline Note 74, treatment with GH for children with conditions such as panhypopituitarism, iatrogenic and other pituitary disorders, as well as gonadal dysfunction, should only continue until adult height, as determined by bone age, is achieved.	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #11
11. Is the request for a pediatric patient with Prader-Willi syndrome who has: • Severe obesity? or • A history of upper airway obstruction or sleep apnea? or • Severe respiratory impairment? Note: Recombinant somatropin is contraindicated in these patients due to the risk of sudden death.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 12
12. Is the requested product preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #13

Initial Approval Criteria		
13. Will the prescriber consider a change to a preferred product that is FDA-approved for the condition? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Go to #14
14. Is the request for lonapegsomatropin?	**Yes:** Go to #15	**No:** Approve for up to 12 months
15. Is the request for a pediatric patient 1 year or older with a body weight >11.5 kg?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in patient prior to reaching adulthood (<18 years of age)?	**Yes:** Go to #3	**No:** Go to #5
3. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for isolated human growth hormone deficiency in an adult (E23.0), short stature due to an endocrine disorder (E34.3), or another unfunded condition?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #6
6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7

7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

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

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

Drug Class Literature Scan: Bile Therapy

Date of Review: December 2021

Date of Last Review: November 2019
Literature Search: 02/01/2017 – 09/16/2021

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

Conclusions:

- Since the last bile acid class review, 3 high-quality systematic reviews[1-3] and 2 high-quality clinical guidelines[4,5] were published.
- A 2020 Cochrane Review evaluated pharmacological interventions in patients with intrahepatic cholestasis of pregnancy (ICP).[1] Specific outcomes included maternal pruritus and adverse fetal impact.[1] The pruritus score is measured on a 100 mm visual analogue scale (VAS) where a score of zero indicates no itch and a score of 100 mm indicates severe itching.[1] In one RCT, a change of 30 mm on the VAS was considered clinically meaningful by the researchers and study participants.[6] There is no evidence this score has been validated to establish a minimal clinically important difference. Compared with placebo, ursodeoxycholic acid (ursodiol) probably results in a small, but clinically insignificant improvement in pruritus associated with ICP (mean difference [MD] −7.64 points, 95% CI −9.69 to −5.60 points; 2 trials, n=715, moderate-quality evidence).[1] The evidence for fetal distress and stillbirth were uncertain, due to serious limitations in study design and imprecision (risk ratio (RR) 0.70, 95% CI, 0.35 to 1.40 and RR 0.33, 95% CI, 0.08 to 1.37; 6 trials, n=955, low-quality evidence, respectively).[1] There is insufficient evidence to indicate if activated charcoal, dexamethasone, or cholestyramine are effective in treating patients with ICP.[1]
- A 2019 meta-analysis of 2 low-quality studies evaluated the clinical outcomes of the combination therapy of ursodeoxycholic acid and obeticholic acid compared with ursodeoxycholic acid monotherapy in patients with primary biliary cholangitis (PBC).[2] The co-primary endpoints for the 2 RCTs were 1) less than 1.67 times the upper limit of normal (ULN) of serum alkaline phosphatase with 15% reduction from baseline and 2) serum total bilirubin within normal limits at the completion of the trials (85 days and 12 months).[2] Fifty-two percent of patients in the combination therapy groups and 22% in the monotherapy groups met both of the endpoints, but there were no statistically significant differences between the groups (RR 2.75; 95% CI, 0.43 to 17.68, p=0.29).[2] Secondary outcomes of interest included liver biochemistry parameters including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT), and conjugated bilirubin. The results of this meta-analysis indicate that combination therapy was significantly superior to monotherapy in reducing serum ALT (MD -15.63 IU/L; 95% CI, –21.59 to –9.68), AST (MD –6.63 IU/L; 95% CI, –11.03 to –2.24), and GGT (MD –131.30 IU/L; 95% CI, –177.52 to –85.08).[2] However, there was no significant difference between combination therapy groups and monotherapy groups for reducing conjugated bilirubin (MD –0.06 mg/dL; 95% CI, –0.28 to 0.15; p=0.56).[2] The results of this analysis indicated that combination therapy did not differ significantly from monotherapy in improving primary endpoints or reducing bilirubin, but was statistically significantly superior to monotherapy in reducing liver biochemical parameters.[2] The results of this meta-analysis are limited by the small number of low-quality trials that were available for inclusion and assessment. There is a need for high-quality RCTs that evaluate the safety and efficacy of combination ursodeoxycholic acid and obeticholic acid in patients with PBC who have an inadequate response to ursodeoxycholic acid monotherapy.[2]

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- A 2021 systematic review analyzed the safety and efficacy of obeticholic acid as treatment for non-alcoholic steatohepatitis (NASH), PBC, and primary sclerosing cholangitis (PSC).[3] Currently, there are no FDA-approved pharmacotherapy options to treat NASH or PSC. Ursodeoxycholic acid and obeticholic acid are FDA-approved as treatments for patients with PBC. Obeticholic acid 10 mg and 25 mg doses improved fibrosis in NASH patients, but neither dose was associated with steatosis improvement.[3] The use of 25 mg obeticholic acid resulted in higher treatment discontinuation rates and significant risk of pruritus.[3] Obeticholic acid treatment led to a significantly better response than the placebo in patients with PBC (OR 4.5, 95% CI, 2.74 to 7.4, $p<0.001$, $I^2 = 40.67$).[3] With the 10 mg obeticholic acid dose, the odds of improvement was 1.61 (95% CI, 1.03-2.51; $p=0.03$), while with the 25 mg dose, it was 2.23 (95% CI, 1.55-3.18; $p<0.001$).[3] The alkaline phosphatase response was better at lower doses (5 to 10 mg) than at higher doses of obeticholic acid (25 to 50 mg).[3] One RCT showed a significant reduction in alkaline phosphatase levels in PSC patients treated with obeticholic acid without the added risk of pruritus; however, further studies are required to validate the findings.[3]
- In April 2017, the National Institute for Health and Care Excellence (NICE) published guidance for the use of obeticholic acid for treating PBC.[4] Obeticholic acid is recommended as an option for treating PBC in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid alone, or as monotherapy for people who cannot tolerate ursodeoxycholic acid.[4] Response to obeticholic acid should be assessed after 12 months with continuation only if there is evidence of clinical benefit.[4]
- The British Society of Gastroenterology (BSG) Liver Section and United Kingdom (UK)-PBC published guidance for PBC treatment and management in 2018.[5] Pharmacotherapy recommendations include:
    - Oral ursodeoxycholic acid is recommended at 13 to 15 mg/kg/day as the first-line pharmacotherapy in all patients with PBC. If tolerated, treatment should usually be life-long. (Strong Recommendation; High Quality of Evidence)[5]
    - In patients with inadequate response or intolerance to ursodeoxycholic acid as defined by alkaline phosphatase > 1.67 x ULN and/or elevated bilirubin 2 x ULN, the addition of obeticholic acid has been associated with improvements in biochemical surrogates of disease activity reasonably likely to predict improved outcomes.[6] Therefore, in keeping with the NICE evaluation of obeticholic acid, it is recommended the addition of obeticholic acid for patients with an inadequate response or intolerance to ursodeoxycholic acid, is considered.[6] (Strong Recommendation; Low Quality of Evidence).[5]
- The FDA issued a drug safety communication on September 21, 2017 regarding the increased risk of hepatic injury and death due to incorrect dosing of obeticholic acid.[7] As a result of this FDA alert, the manufacturer added a boxed warning in February 2018 regarding risk of hepatic decompensation and failure in incorrectly dosed PBC patients with Child-Pugh Class B or C or decompensated cirrhosis.[8] The recommended dosing for patients with impaired hepatic function at that point in time was 5 mg once a week.[8] The FDA issued a stronger safety advisory in May 2021 stating that due to the risk of serious hepatic injury, the use of obeticholic acid must be restricted in PBC patients with advanced cirrhosis.[9] The manufacturer strengthened the boxed warning regarding risk of fatal hepatic injury to obeticholic acid prescribing information in May 2021.[10] Obeticholic acid is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended at this time.
- Modify obeticholic acid prior authorization(PA) criteria (**Appendix 4**) to include recommended dosing parameters and safety precautions to avoid serious hepatic injury.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy:
Obeticholic acid, which is indicated for treatment of PBC, was reviewed by the Pharmacy and Therapeutics (P & T) Committee at the January 2017 meeting. After discussion, the P & T Committee made the following recommendations:

- Incorporate bile therapy drugs (obeticholic acid, ursodeoxycholic acid [ursodiol], and cholic acid) into one PDL class within the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Designate ursodiol as a preferred medication and obeticholic acid as a non-preferred medication due to the lack of long-term efficacy and safety data.
- Approve PA criteria (**Appendix 4**) for all non-preferred drugs which encourages use of ursodiol as first-line therapy and restricts obeticholic acid use to populations that may benefit from this therapy without undue harm.

At the November 2019 P & T Committee meeting, the efficacy and safety of cholic acid for treatment of bile acid synthesis disorders and peroxisomal disorders (Zellweger spectrum disorders) were evaluated. After review, cholic acid was designated as a non-preferred agent on the PDL and PA criteria for cholic acid (**Appendix 4**) were implemented to ensure use according to FDA-approved indications.

Appendix 1 describes the PDL status of the different bile therapy drugs. Currently, ursodiol is preferred and all the other agents are non-preferred with PA required before utilization in Medicaid Fee-For-Service (FFS) patients. In the second quarter of 2021, most of the FFS utilization in the bile salt class resulted from claims for ursodiol (87%). There was minimal utilization of cholic acid (13%). No claims were submitted for obeticholic acid.

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:
Cochrane Review: Pharmacological Interventions For Treating Intrahepatic Cholestasis Of Pregnancy
A 2020 Cochrane Review focused on the evidence of pharmacological interventions to treat patients with ICP on maternal, fetal and neonatal outcomes.[1] The 2020 publication was an update of prior Cochrane reviews on this topic. Intrahepatic cholestasis of pregnancy is a liver disorder which appears most often in the third trimester.[1] It is a relatively benign though often very distressing condition for the patient, but it may adversely affect fetal outcome, as seen by associations with preterm labor, fetal distress and stillbirth, particularly in severe cases.[1] The diagnosis of ICP is based on a combination of pruritus and increased concentrations of serum bile acids (values usually at least 10 µmol/L). Pruritis classically affects palms and soles but may become generalized, though without a rash apart from excoriations.[1] Increased concentrations of serum transaminases (e.g. ALT greater than 50 U/L) are often seen.[1] The incidence may vary across ethnic groups. It has been reported in fewer than 1% of pregnancies in Central and Western Europe, North America and Australia, in 1% to 2% in Scandinavia and

the Baltic states, but can be as high as 5% to 15% in Araucanian Indians in Chile and Bolivia.[11] Since the pathophysiology is poorly understood, therapies have been largely empiric.[1] As ICP is an uncommon condition (incidence less than 2% a year), many trials have included small numbers of participants.[1]

Literature for the 2020 update was searched through December 2019. Twenty-six trials involving 2,007 women met inclusion criteria.[1] Two placebo-controlled trials of ursodeoxycholic acid in 715 women were judged as having a low risk of bias.[1] The pruritus score is measured on a 100 mm VAS where a score of zero indicates no itch and a score of 100 mm indicates severe itching.[1] In one RCT, a change of 30 mm on the VAS was considered clinically meaningful by the researchers and study participants.[6] There is no evidence this score has been validated to establish a minimal clinically important difference. Compared with placebo, ursodeoxycholic acid probably results in a small, but clinically insignificant improvement in pruritus (MD −7.64 points; 95% CI, −9.69 to −5.60 points; moderate-quality evidence).[1] The evidence for fetal distress and stillbirth were uncertain, due to serious limitations in study design and imprecision (RR 0.70; 95% CI, 0.35 to 1.40 and RR 0.33; 95% CI, 0.08 to 1.37; respectively, 6 trials; 955 women; low quality evidence).[1]

There is insufficient evidence to indicate if activated charcoal, dexamethasone, or cholestyramine are effective in treating women with ICP.[1] When compared with placebo, ursodeoxycholic acid administered to women with ICP shows a slight reduction in pruritus.[1] For most pregnant patients and clinicians, the reduction may fall below the minimum clinically worthwhile effect.[1] The evidence was unclear for other adverse fetal outcomes, due to low-certainty evidence.[1]

Combination Obeticholic Acid And Ursodeoxycholic Acid In Patients With Primary Biliary Cholangitis Who Respond Incompletely To Ursodeoxycholic Acid

The aim of this 2019 meta-analysis was to evaluate the clinical outcomes of the combination therapy of ursodeoxycholic acid and obeticholic acid compared with ursodeoxycholic acid monotherapy in patients with PBC.[2] The literature search was conducted through September 2018. Primary biliary cholangitis is a rare, chronic, autoimmune cholestatic liver disease that predominantly occurs in middle-aged women.[2] Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age.[12] On the basis of data from case-finding studies, a latitudinal geoepidemiological pattern of occurrence of primary biliary cirrhosis has been proposed, with the disease being most frequent in northern Europe and North America.[13] The highest prevalence and incidence rates have been reported in Scandinavia, Great Britain, and the northern Midwest region of the United States.[13] Approximately 50 to 60 percent of patients with PBC are asymptomatic at diagnosis and are detected because of abnormalities in liver biochemical tests obtained for other reasons.[14] Among patients with symptoms, fatigue and pruritus are most commonly seen. In newly diagnosed patients, approximately one-half complain of fatigue and one-third pruritus.[12] The progressive destruction of small intrahepatic bile ducts, resulting in the development of fibrosis and potential cirrhosis is a unique feature of PBC.[2] Serum alkaline phosphatase and bilirubin are strongly associated with clinical outcomes (death or liver transplantation) in patients with PBC.[2]

Two studies (n=222) met inclusion criteria and were included in the meta-analysis.[2] The population included patients with PBC who incompletely responded to ursodeoxycholic acid (13–15 mg/kg/day).[2] These patients were randomly assigned to receive obeticholic acid at different doses (5 to 25 mg/day). The mean patient age was 54.9 years and the ratio of male to female was 1:13.[2] The duration of treatment of these two trials was 85 days and 12 months, respectively.[2] The two trials included in the meta-analysis were considered low quality as there are high or unclear risks for bias for at least one component of the Cochrane risk of bias assessment.[2]

The co-primary endpoints for the 2 RCTs were 1) less than 1.67 times the ULN of serum alkaline phosphatase with 15% reduction from baseline and 2) serum total bilirubin less than the ULN at the end of trials.[2] Fifty-eight of 111 patients (52%) in the combination therapy groups and 24 of 111 patients (22%) in the monotherapy groups had the primary endpoints, but there were no significant differences between the groups (RR 2.75; 95% CI, 0.43 to 17.68; p=0.29).[2] Secondary outcomes of interest included liver biochemistry parameters including serum ALT, AST, GGT, and conjugated bilirubin. The results of this meta-analysis indicate that combination therapy was significantly superior to monotherapy in reducing serum ALT (MD 15.63 IU/L; 95% CI, –21.59 to –9.68), AST (MD –

6.63 IU/L; 95% CI, –11.03 to –2.24), and GGT (MD –131.30 IU/L; 95% CI, –177.52 to –85.08).[2] However, there was no significant difference between combination therapy groups and monotherapy groups for reducing conjugated bilirubin (MD –0.06 mg/dL; 95% CI, –0.28 to 0.15; p=0.56).[2] No significant association with increased risks of adverse events was found between patients with combination therapy versus monotherapy.[2] The results of this study indicate that combination therapy did not differ significantly from monotherapy in improving primary endpoints, conjugated bilirubin, or adverse events, but was superior to monotherapy in reducing liver biochemical indices including ALT, AST, and GGT.[2] The results of this meta-analysis are limited by the small number of low-quality trials that were available for inclusion and assessment. There is a need for high-quality RCTs that evaluate the safety and efficacy of combination ursodeoxycholic acid and obeticholic acid in patients with PBC who have an inadequate response to ursodeoxycholic acid monotherapy.[2]

Efficacy And Safety Of Obeticholic Acid In Liver Disease

A 2021 systematic review and meta-analysis analyzed the safety and efficacy of obeticholic acid as treatment for non-alcoholic steatohepatitis (NASH), PBC, and PSC.[3] Literature was searched from January 2000 through March 2020. Currently, there are no FDA-approved pharmacotherapy options to treat NASH or PSC. Ursodeoxycholic acid and obeticholic acid are FDA-approved as treatments for patients with PBC. Outcomes of interest included histological improvement in NASH (fibrosis and steatosis), reduction in alkaline phosphatase (less than 1.67 the ULN) in patients with PBC, mean reduction in alkaline phosphatase levels in patients with PSC, and the adverse effects of obeticholic acid (pruritus and drug discontinuation). Seven RCTs (n=2834) conducted in adults met inclusion critiera.[3] Three RCTs (n=2317) were in patients with NASH, 3 RCTs (N=441) were in PBC patients, and 1 RCT (N=76) in patients with PSC.[3] The methodological quality of the included studies was of moderate to high quality.[3] All the included trials were placebo-controlled RCTs, reported complete data, and had low heterogeneity.[3] The main limitation of this meta-analysis is the small number of studies for each hepatic disease.[3]

Three RCTs evaluated fibrosis improvement in NASH. Three hundred twelve patients received 10 mg obeticholic acid, 410 patients received 25 mg obeticholic acid, and 720 patients received placebo.[3] The studies were conducted over 52 to 72 weeks. The meta-analysis showed fibrosis improvement was significantly better in NASH patients who received either dose of obeticholic acid compared to patients in the placebo group (OR 1.95; 95% CI, 1.47 to 2.59; p<0.001; $I^2 = 0$).[3] With the 10 mg obeticholic acid dose, the odds of improvement was 1.61 (95% CI, 1.03-2.51; p=0.03), while with the 25 mg dose, it was 2.23 (95% CI, 1.55-3.18; p<0.001).[3] There was no significant effect on steatosis with either 10 mg or 25 mg dose of obeticholic acid (OR 1.19; 95% CI, 0.88 to 1.6; p=0.24).[3] However, 25 mg obeticholic acid led to significant adverse events and discontinuation of the drug (OR 2.8; 95% CI 1.42 to 3.02; p<0.001) compared with 10 mg obeticholic acid (OR 0.95; 95% CI 0.6 to 1.5; p=0.84).[3]

Three studies on patients with PBC reported a response to obeticholic acid (alkaline phosphatase 1.67 ULN or less).[3] One hundred thirty-one patients were treated with obeticholic acid 10 mg, 70 patients received 5 mg, 48 patients received 25 mg, and 57 patients received 50 mg, compared to 134 patients who received placebo.[3] Obeticholic acid treatment led to a significantly better response than the placebo in patients with PBC (OR 4.5; 95% CI, 2.74 to 7.4; p<0.001, $I^2 = 40.67$).[3] The alkaline phosphatase response was better at lower doses (5 to 10 mg) than at higher doses of obeticholic acid (25 to 50 mg).[3] The response to 5 mg obeticholic acid was an OR of 7.66 (95% CI, 3.12 to 18.81; p<0.001), 10 mg was 5.18 (95% CI, 2 to 13.41; p=0.001), 25 mg was 2.36 (95% CI, 0.94 to 5.93; p=0.06) and 50 mg was 4.08 (95% CI 1.05 to 15.78; p=0.04).[3]

Only one phase 2, dose-finding study reported on the safety of obeticholic acid in PSC.[3] The dose of obeticholic acid was increased from 1.5 to 3 mg or 5 mg increased to 10 mg after 3 months of therapy.[3] The median dose of obeticholic acid was 5 mg. At 6 months, the mean reduction in alkaline phosphatase compared to placebo was −80.97 IU/L (95% CI, −137.84 to −24.05; p=0.005).[3] Nearly 50% of patients received concomitant ursodeoxycholic acid therapy. However, the magnitude of alkaline phosphatase reduction was greater in patients who did not receive ursodeoxycholic acid (25−30% reduction) than in those

who did receive ursodeoxycholic acid (15% reduction), and the reason for this is unknown.[3] Further studies are required to validate the findings from this single phase 2 trial.

Compared with placebo, obeticholic acid increased the odds of pruritus in all 3 cholestatic liver diseases by 2.3 times (95% CI, 1.56 to 3.4; p<0.001).[3] In NASH patients, the 25 mg obeticholic acid dose increased the odds of pruritus by 3.93 times (95% CI, 2.0 to 7.38, p<0.001), while the 10 mg obeticholic acid dose increased the odds of pruritus 1.65 times (95% CI, 1.27 to 2.14; p<0.001) compared to placebo.[3] In NASH, the odds of discontinuation seemed to be similar in those with 10 mg obeticholic acid and placebo (OR 0.95; 95% CI, 0.6 to 1.5; p=0.84).[3] However, with 25 mg obeticholic acid, the odds of discontinuation of the drug were higher than those with the placebo (OR 2.8; 95% CI, 1.42 to 3.02; p<0.001).[3 3]

After review, 3 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).[15-17]

New Guidelines:
High Quality Guidelines:
National Institute for Health and Care Excellence
NICE guidance published in April 2017 provided evidence-based recommendations for the use of obeticholic acid in treatment of adults with PBC.[4] The committee considered the clinical evidence for obeticholic acid plus ursodeoxycholic acid compared with ursodeoxycholic acid plus placebo from the POISE trial, and obeticholic acid monotherapy compared with placebo for adults who cannot tolerate ursodeoxycholic acid.[4] People who took part in POISE were mainly women (91%) and younger than 65 years (81%).[4] Inclusion criteria included a serum alkaline phosphatase level of at least 1.67 times the upper limit of normal, and/or elevated total bilirubin level above the upper limit of normal.[4] A small number of patients (n=11) in the trial could not tolerate ursodeoxycholic acid.[4] A higher number of people were classified as responders according to the primary outcome in POISE for obeticholic acid plus ursodeoxycholic acid compared with placebo plus ursodeoxycholic acid (47% in the obeticholic acid 10 mg group and 46% in the obeticholic acid titration group compared with 10% in the placebo group, p<0.0001 for both comparisons).[4] Obeticholic acid plus ursodeoxycholic acid was also more effective at lowering alkaline phosphatase levels by at least 40% from the baseline (34% in the obeticholic acid 10 mg group and 30% in the obeticholic acid titration group, compared with 1% in the placebo group).[4] Obeticholic acid plus ursodeoxycholic acid was more effective at lowering the total bilirubin level, which at 12 months was 9.7 mg/dL for the obeticholic acid 10 mg group, 9.9 mg/dL for the obeticholic acid titration group, and 13.2 mg/dL for the placebo group.[4] The committee concluded that obeticholic acid plus ursodeoxycholic acid is clinically effective in improving the surrogate outcomes associated with the progression of PBC.[4] Pruritus was the most common adverse event with obeticholic acid, occurring in 66% of patients taking 10 mg, and 50% of patients taking 5 mg, compared with 37% in the placebo arm.[4]
NICE pharmacotherapy recommendations are as follows:

- Obeticholic acid is recommended as an option for treating PBC in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.[4]
- The starting dose of obeticholic acid is 5 mg once daily. Based on assessment of tolerability after 3 months, the dose should be increased to 10 mg once daily for optimal response.[4]
- Assess the response to obeticholic acid after 12 months. Only continue therapy if there is evidence of clinical benefit.[4]

The British Society of Gastroenterology and United Kingdom Primary Biliary Cholangitis Council
The BSG Liver Section and UK-PBC Council published guidance for PBC treatment and management in 2018.[5] UK-PBC is a Medical Research Council-funded rare disease medical initiative which provides support to providers, patients, and researchers for managing PBC.[5] Members of the guideline writing committee

included gastroenterologists, hepatologists, transplant physicians, liver pathologists and patient representatives.[5] The guidelines were produced using a systematic review of publications identified searches in line with the Appraisal of Guidelines Research & Evaluation II (AGREE II) instrument.[5]
In PBC, a dose of ursodeoxycholic acid 13 to 15 mg/kg/day has been shown to be superior to 5 to 7 mg/kg/day or 23 to 25 mg/kg/day.[5] Three large double-blind randomized trials used the same dose of ursodeoxycholic acid (13–15 mg/kg/day), and the results have been analyzed according to an intention-to-treat principle.[5] Ultimately, this combined analysis of the three trials (548 patients) showed a one-third reduction in the risk of death or transplant for patients with moderate to severe PBC.[5] Ursodeoxycholic acid at the recommended dose is very safe with minimal side effects (weight gain of 3 kg in the first 12 months, hair loss and, rarely, diarrhea and flatulence are reported).[5] There are no data to suggest that ursodeoxycholic acid is teratogenic.[5]

Relevant trial data to support safety and efficacy of obeticholic acid are from studies spanning phase 2 and 3 drug development.[5] In a phase 2 randomized, double-blind, controlled trial of obeticholic acid in PBC, the therapeutic efficacy of three doses (10, 25 and 50 mg/day) as add-on therapy to ursodeoxycholic acid in patients having persistent elevations in serum alkaline phosphatase (>1.5 × ULN) was evaluated.[5] The primary endpoint was a significant reduction in serum alkaline phosphatase from baseline, and was met across all three doses of obeticholic acid versus placebo.[5] In a phase 3 clinical trial, patients with high-risk PBC (alkaline phosphatase >1.67 x ULN and/or elevated total bilirubin >2 x ULN) were evaluated in a placebo controlled RCT.[5] The primary endpoint during the 12-month double-blind period was attainment of both an alkaline phosphatase value <1.67 × ULN (with a ≥15% reduction from baseline) and a normal serum bilirubin.[5] In an intention-to-treat analysis, biochemical response was met in 10% of the placebo group and in 47% and 46% in the 10 mg and 5–10 mg dose-titrated obeticholic acid groups, respectively (P<0.0001 for both).[5] The mean decrease in serum alkaline phosphatase from baseline was 39% and 33% in the 10 mg and titrated OCA groups, respectively, versus 5% for patients in the placebo group (P<0.0001 for both).[5]

Treatment with obeticholic acid is associated with a dose-dependent exacerbation in pruritus leading to treatment discontinuation in 1–10% of patients.[5] These observations emphasize the importance of dose titration for symptom control.[5] Obeticholic acid-treated patients may also exhibit (reversible) alterations in serum lipid levels, most notably a small decrease in HDL.[5] It is not yet known whether these changes impact the long-term cardiovascular risk.[5]

Specific pharmacotherapy recommendations for PBC include:

- Oral ursodeoxycholic acid is recommended at 13–15 mg/kg/day as the first-line pharmacotherapy in all patients with PBC. If tolerated, treatment should usually be life-long (Strong Recommendation; High Quality of Evidence).[5]
- In patients with inadequate response or intolerance to ursodeoxycholic acid as defined by alkaline phosphatase >1.67 x ULN and/or elevated bilirubin 2 x ULN, the addition of obeticholic acid has been associated with improvements in biochemical surrogates of disease activity reasonably likely to predict improved outcomes.[5] Therefore, in keeping with the NICE evaluation of obeticholic acid, it is recommended the addition of obeticholic acid for patients with an inadequate response to ursodeoxycholic acid or intolerant of ursodeoxycholic acid, be considered.[5] Dose adjustment in patients with advanced liver disease as per the drug label is recommended. (Strong Recommendation; Low Quality of Evidence)[5]

After review, 1 guideline was excluded due to poor quality.[18]

New FDA Safety Alerts:
The FDA issued a drug safety communication on September 21, 2017 regarding the increased risk of hepatic injury and death due to incorrect dosing of obeticholic acid.[7] Some patients received excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label.[7] Nineteen cases of death were identified, of which 8 provided information about the patient's cause of death.[7] The cause of death was reported to be worsening of PBC disease in seven cases, with cardiovascular disease cited in the other cases.[7] Seven of these 8 cases described patients with moderate to severe decreased liver function

who received obeticholic acid 5 mg daily, instead of a dose no greater than 10 mg twice weekly as recommended in the label prescribing information for patients with this extent of decreased liver function.[7] FDA also identified 11 cases of serious liver injury with obeticholic acid use.[7] Six of the patients who had moderate or severe decreases in liver function at baseline and developed serious liver injury were receiving obeticholic acid 5 mg daily, instead of a dose no greater than 10 mg twice weekly as recommended by FDA in the drug label at that time.[7] Three of these 6 patients died, which were included in the 19 death cases mentioned previously.[7] Obeticholic acid was discontinued in 4 of 6 cases, which resulted in one patient experiencing symptom resolution and an improvement in a liver blood test.[7] The remaining three cases did not report the response after discontinuation.[7] The other five cases of serious liver injury were reported in patients with no or mild decreases in liver function prior to initiating obeticholic acid.[7] Four of these five patients received obeticholic acid 5 mg daily, and one did not report the dose.[7] Obeticholic acid was discontinued in all 5 cases, which resulted in one patient experiencing symptom resolution and one patient experiencing improved liver blood tests and symptom resolution.[7] As a result of this FDA alert, the manufacturer added a boxed warning in February 2018 regarding risk of hepatic decompensation and failure in incorrectly dosed PBC patients with Child-Pugh Class B or C or decompensated cirrhosis.[8] The recommended dosing for patients with impaired hepatic function at that point in time was 5 mg once a week.[8]

The FDA issued a stronger safety advisory in May 2021 stating that due to the risk of serious hepatic injury, the use of obeticholic acid must be restricted in PBC patient with advanced cirrhosis.[9] In the 5 years since obeticholic acid's accelerated approval, FDA identified 25 cases of serious liver injury leading to liver decompensation or liver failure associated with obeticholic acid in PBC patients with cirrhosis, both in those without clinical signs of cirrhosis (compensated) or in those with clinical signs of cirrhosis (decompensated).[9] Many of these PBC patients had advanced cirrhosis before starting obeticholic acid.[9] The 25 cases include only those submitted to FDA and those found in the medical literature, so there may be additional cases about which the FDA is unaware.[9] All of these patients were taking obeticholic acid at recommended dosages.[9] After starting obeticholic acid, the pace of the liver decompensation or failure reported suggested these adverse events, which resulted in liver transplant in a small number of cases, were related to the drug rather than progression of the underlying PBC.[9] The manufacturer strengthened the boxed warning regarding risk of fatal hepatic injury to obeticholic acid prescribing information in May 2021.[10] Obeticholic acid is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10]

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)
Obeticholic Acid	OCALIVA	2/2018	Boxed Warning	WARNING: HEPATIC DECOMPENSATION AND FAILURE IN INCORRECTLY DOSED PBC PATIENTS WITH CHILD-PUGH CLASS B OR C OR DECOMPENSATED CIRRHOSIS[8] • In Postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with PBC with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCALIVA was dosed more frequently than recommended.[8] • The recommended starting dosage of OCALIVA is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event.[8]

Obeticholic Acid	OCALIVA	5/2021	Boxed Warning	WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS[10] • Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in PBC patients with either compensated or decompensated cirrhosis.[10] • OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension(e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).[10] • Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment.[10]

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3. Kulkarni AV, Tevethia HV, Arab JP, et al. Efficacy and safety of obeticholic acid in liver disease-A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol.* 2021;45(3):101675.
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9. Food and Drug Administration (FDA) Drug Safety Communication. https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis. May 21, 2021. Accessed October 11, 2021.
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12. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med.* 2005;353(12):1261-1273.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
ursodiol	ACTIGALL	ORAL	CAPSULE	Y
ursodiol	URSODIOL	ORAL	CAPSULE	Y
ursodiol	URSO	ORAL	TABLET	Y
ursodiol	URSO FORTE	ORAL	TABLET	Y
ursodiol	URSODIOL	ORAL	TABLET	Y
cholic acid	CHOLBAM	ORAL	CAPSULE	N
obeticholic acid	OCALIVA	ORAL	TABLET	N
ursodiol	RELTONE	ORAL	CAPSULE	N
chenodiol	CHENODAL	ORAL	TABLET	Not reviewed
dehydrocholic acid	DECHOLIN	ORAL	TABLET	Not reviewed

Appendix 2: New Comparative Clinical Trials

A total of 29 citations were manually reviewed from the initial literature search. After further review, 29 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 September Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to September 16, 2021

1.	Cholangitis/ or Non-alcoholic Fatty Liver Disease or Liver Cirrhosis, Biliary	23317
2.	Chenodeoxycholic Acid/ or "Bile Acids and Salts"/ or Ursodeoxycholic Acid/	12975
3.	Ursodeoxycholic Acid/	2952
4.	Cholic Acid	784
5.	obeticholic acid.mp.	457
6.	Dehydrocholic Acid/	37
7.	odexvixibat.mp	2
8.	Cholestasis, Intrahepatic/ or Biliary Atresia/	5344
9.	1 and 8	292
10.	2 or 3 or 4 or 5 or 6 or 7	13548
11.	9 and 10	29

Appendix 4: Prior Authorization Criteria

Cholic Acid (Cholbam™)

Goal(s):

- To ensure appropriate use of cholic acid in patients with bile acid synthesis disorders (BASDs) due to a single enzyme defects (SEDs) or as an adjunct to patients with peroxisomal disorders (PD), including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

Length of Authorization:

- Up to 12 months

Requires PA:

Cholic acid

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 cholic acid prescribed by a hepatologist or pediatric gastroenterologist?	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has baseline hepatic function been assessed? *The manufacturer recommends providers to monitor aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and international normalized ratio (INR) every month for the first 3 months of therapy, every 3 months for the next 9 months, every 6 months during the next 3 years and annually thereafter.[1]	**Yes:** Approve for 3 months. Document baseline hepatic function values (AST,ALT, Alk Phos, bilirubin) and date obtained:_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of improvement of primary biliary cholangitis, defined as: a. ALP <1.67-times the ULN; AND b. Decrease of ALP >15% from baseline: AND ~~a.~~c. Normal total bilirubin level?	**Yes:** Document ALP and total bilirubin level. Go to # 2 ALP:_____units/L Total Bilirubin _____mg/dL	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Has the patient's condition stabilized or improved as assessed by the prescribing provider?	**Yes:** Approve for 12 months.	**No**: Pass to RPh. Deny; medical appropriateness

1. Cholbam (cholic acid) capsules [Full Prescribing Information]. San Diego, CA: Retrophin, Inc. March 2015.

P&T/DUR Review: 12/21 (DM); 11/19 (DM)
Implementation: 1/1/2020

Obeticholic Acid (Ocaliva®)

Goal(s):

- Encourage use of ursodiol or ursodeoxycholic acid which has demonstrated decrease disease progression and increase time to transplantation.
- Restrict use to populations for which obeticholic acid has demonstrated efficacy.

Length of Authorization:

- Up to 12 months

Requires PA:

- Obeticholic acid

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 request for continuation of therapy previously approved by the FFS program (patient has already been on obeticholic acid)?	**Yes:** Go to Renewal Criteria	**No:** Go to #3

Approval Criteria		
3. Is the treatment for an adult with primary biliary cholangitis ~~or cirrhosis (PBC~~either: • without cirrhosis OR • with compensated cirrhosis who do not have evidence of portal hypertension (e.g. ascites, gastroesophageal varices, persistent thrombocytopenia)~~)~~?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
~~4.Does the patient have no evidence of complications from cirrhosis or hepatic decompensation (e.g., MELD score less than 15; not awaiting transplant; no portal hypertension; or no hepatorenal syndrome)?~~	~~**Yes:** Go to #5~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~5.Is the total bilirubin level less than 2-times the upper limit of normal (ULN)?~~	~~**Yes:** Go to #6~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
4. Does patient have a documented intolerance or contraindication to ursodiol?	**Yes:** Document symptoms of intolerance or contraindication and go to #6.~~approve for up to 12 months~~	**No:** Go to #5
5. Has patient had a 12-month trial of ursodiol with inadequate response to therapy (Alkaline phosphatase [ALP] ≥1.67-times the ULN or total bilirubin greater than the ULN)?	**Yes**: Document baseline ALP and total bilirubin level and go to # 6 ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is obeticholic acid dosed according to the guidelines outlined in Table 1?	**Yes:** Approve for 12 months	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of improvement of primary biliary cholangitis, defined as: a. ALP <1.67-times the ULN; AND b. Decrease of ALP >15% from baseline: AND c. Normal total bilirubin level?	**Yes**: Document ALP and total bilirubin level go to # 2 ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness
2. Does dosing meet parameters outlined in Table 1?	**Yes**: Approve for up to 12 months	**No**: Pass to RPh. Deny; medical appropriateness

Table 1. Obeticholic Acid Dosing Regimen by Patient Population[1]

Staging/Classification	Non-Cirrhotic or Compensated Child-Pugh Class A	Patients with Intolerable Pruritus*	Decompensated cirrhosis (Child-Pugh Class B or C OR~~or~~ Patients with a Prior Decompensation Event)(e.g., ascites, gastroesophageal varices, persistent thrombocytopenia).
Initial dose for first 3 months	5 mg once daily	5 mg every other day for patients intolerant to 5 mg once daily 5 mg once daily for patients intolerant to 10 mg once daily Temporarily interrupt administration for 2 weeks. Restart at reduced dosage.	**Obeticholic acid therapy is contraindicated in these patients.**
Dose titration after first 3 months for patients who have not achieved adequate reduction in ALP and/or total bilirubin and who are tolerating obeticholic acid	10 mg once daily		
Maximum dose	10 mg once daily	5 mg once daily	

*Add an antihistamine or bile acid binding resin

1. OCALIVA (obeticholic acid) oral tablet Prescribing Information. New York, NY; Intercept Pharmaceuticals, Inc. May 2021.

P&T / DUR Review: *12/21 (DM); 01/17 (SS)*
Implementation: *4/1/17*