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, June 1, 2023 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	A. Gibler (OHA)
	E. Legislative Update	D. Weston (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. Quarterly Utilization Reports	
	B. Oncology Prior Authorization Updates	
	C. Orphan Drug Policy Updates	
	1. Public Comment	
1:25 PM	III. DUR ACTIVITIES	
	A. ProDUR Report	L. Starkweather (Gainwell)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)
	1. Hormone Replacement Therapy – A Focus on the Benefits and Risks of Estrogen	
	2. Pharmacological Prevention and Treatment of Mpox	
	3. Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Benefit for Children and Adolescents	
1:45 PM	D. Pharmacy and Therapeutic Operating Procedures	S. Fletcher (OSU)
	1. Updates to Procedures	
1:50 PM	E. Evaluation of Evidence Methods	
	1. Mental Health Clinical Advisory Group Methods	A. Gibler (OHA)
	2. Pharmacy & Therapeutics Committee Methods	S. Fletcher (OSU)

IV. DUR NEW BUSINESS

2:05 PM

A. Low-Dose Quetiapine Drug Use Evaluation
   1. Mental Health Clinical Advisory Group Summary — A. Gibler (OHA)
   2. Drug Use Evaluation/Prior Authorization Criteria — S. Servid (OSU)
   3. Public Comment
   4. Discussion and Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

2:25 PM

A. Skyclarys™ (omaveloxolone) New Drug Evaluation — D. Moretz (OSU)
   1. New Drug Evaluation/Prior Authorization Criteria
   2. Public Comment
   3. Discussion and Clinical Recommendations to OHA

2:40 PM

B. CGRP Inhibitors DERP Summary — D. Engen (OSU)
   1. DERP Summary/Prior Authorization Criteria
   2. Public Comment
   3. Discussion and Clinical Recommendations to OHA

3:00 PM BREAK

3:15 PM

C. Severe Inflammatory Skin Disease Prior Authorization Update — D. Moretz (OSU)
   1. Prior Authorization Criteria
   2. Public Comment
   3. Discussion and Clinical Recommendations to OHA

3:20 PM

D. Botulinum Toxins Class Update — K. Sentena (OSU)
   1. Class Update/Prior Authorization Criteria
   2. Public Comment
   3. Discussion and Clinical Recommendations to OHA

3:40 PM

E. *Clostridioides difficile* Drugs Class Update — D. Moretz (OSU)
   1. Class Update/Prior Authorization Criteria
   2. Rebyota™ (fecal microbiota, live-jslm) New Drug Evaluation
   3. Public Comment
   4. Discussion and Clinical Recommendations to OHA

4:00 PM VI. EXECUTIVE SESSION

4:50 PM VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, April 6th, 2023
1:00 PM - 4:30 PM
Via Zoom webinar

MEETING MINUTES

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

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

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

Audience: Rushi Parikh, Provention Bio*; Jason Kniffin, Novo Nordisk; Mark Kantor, AllCare Health; Sandee Merrick, Provention Bio; Bill Gittinger, MTPA; Brandie Feger, Advanced Health CCO; Chris Ferrin, Samaritan Health Plans; Gary Parenteau, Dexcom Inc; Lori McDermott, Viking HCS; Mark Wolber, Sunovion; Matt Worthy, OHSU; Melissa Abbott, Eisai; Stuart O'Brochta, Gilead; Nirmal Ghuman; Norman Navarro, Providence; Rushi Paikh, Provention Bio; Saghi Maleki, Takeda Pharmaceuticals; Shauna Wick; Stuart O'Brochta, Gilead; Sydney Wardan, UHA; Erin Nowak, AbbVie; Tiina Andrews, UHA; YJ Shukla, Moda Health EOCCO; Baltazar Diaz, Pacificsource; Melanie Greer, Legacy; Linda Finch, Biogen

(*) Provided verbal testimony

I. CALL TO ORDER

A. Roll Call & Introductions
- Called to order at approx. 1:05 p.m., introductions by Committee and staff

B. Conflict of Interest Declaration – no new conflicts of interest were declared

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C. Approval of Agenda and February 2023 Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor with one abstention

D. Department Update provided by Andrew Gibler, PharmD

E. Legislative Update provided by Dee Weston, JD

II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Orserdu™ (elacestrant); Lunsumio™ (mosunetuzumab-axgb); Adstiladrin® (nadofaragene firadenovec-vncg) and Jaypirca™ (pirtobrutinib) to Table 1 in the Oncology Agents prior authorization (PA) criteria

B. Glaucoma Drugs Class Update & New Drug Evaluation (NDE)
Recommendation:
- No PDL changes recommended based on review of recently published evidence
- Maintain omidenepag as non-preferred on the PDL
- Evaluate costs in executive session

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

III. DUR NEW BUSINESS

A. Generalized Anxiety Disorder (GAD) Update and Pregabalin Drug Use Evaluation: Andrew Gibler, PharmD and Sarah Servid, PharmD
Recommendations:
- Make pregabalin IR capsules preferred
- Update Pregabalin PA criteria to: include GAD; remove gabapentin step therapy for all conditions; and suggest trial of a preferred gabapentinoid product
- Align coverage criteria by removing PA for preferred pregabalin

ACTION: The Committee recommended deferring the topic and asked staff to bring back evidence for safety and efficacy of pregabalin in GAD, and both gabapentin and pregabalin for other diagnoses for Committee to consider before opening coverage
Motion to defer, 2nd, 8 in-favor with one opposed

B. Non-preferred Drugs in Select PDL Classes PA Update: Dave Engen, PharmD
Recommendations:
- Update Non-Preferred Drugs PA criteria to allow approval durations of up to 12 months for patients with a previously approved PA

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

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C. GLP-1 Receptor Agonists for Diabetes Policy Evaluation: Melissa Yokoyama, PharmD
Recommendations:
- Maintain current PA policy
ACTION: Motion to approve, 2nd, all in favor

IV. PREFERRED DRUG LIST (PDL) NEW BUSINESS

A. Tzield™ (teplizumab-mzwv) NDE: Kathy Sentena, PharmD
Recommendations:
- Include with Miscellaneous Antidiabetic Agents class on the PDL and designate as non-preferred
- Implement proposed PA criteria to limit use to people with stage 2 T1DM and high risk of progression to stage 3 T1DM
ACTION: The Committee amended the proposed criteria to add question #4 to deny coverage to those patients who have already progressed to stage 3 T1DM diagnosis; amend question #7 (previously #6) to include dysglycemia as defined by FPG, OGTT, 2-h plasma glucose or HbA1c; and remove the requirement that improvement be documented within one month of the renewal request
Motion to approve, 2nd, all in favor

B. Growth Hormone Focused Class Update for Adults: Dave Engen, PharmD
Recommendations:
- No PDL changes recommended based on review of recently published evidence
- Update PA criteria as proposed
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

C. Circadian Rhythm Sleep-Wake Disorders Indication Review: Sarah Servid, PharmD
Recommendations:
- Continue to require PA to limit use to FDA-labeled and funded indications and update criterion as proposed
- If medically necessary for funded circadian rhythm sleep-wake disorders or if covered under EPSDT, require trial of a melatonin agonist or melatonin before approving sedating drugs and make at least one melatonin agonist preferred
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

D. Amyotrophic Lateral Sclerosis Class Update & NDE: Sara Fletcher, PharmD
Recommendations:
- Designate riluzole as preferred and edaravone and sodium phenylbutyrate-taurursodiol as non-preferred on the PDL
- Implement PA criteria for sodium phenylbutyrate-taurursodiol and update edaravone PA criteria as proposed
- Evaluate costs in executive session

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

V. EXECUTIVE SESSION

Members Present: Pat DeMartino, MD; Douglas Carr, MD; Cat Livingston, MD; Caryn Mickelson, PharmD; Eriko Onishi, MD; Bill Origer, MD; Eddie Saito, PharmD

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

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. Glaucoma Drugs Class Update & NDE
Recommendation: Make brimonidine tartrate 0.1% ophthalmic drops preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Growth Hormone Focused Class Update for Adults
Recommendations: Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Circadian Rhythm Sleep-Wake Disorders Indication Review
Recommendations: Make ramelteon tablets preferred with PA
ACTION: Motion to approve, 2nd, all in favor

D. Amyotrophic Lateral Sclerosis Class Update &NDE
Recommendations: Make riluzole tablets preferred and riluzole film and suspension non-preferred
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2021 - September 2022

Eligibility	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Total Members (FFS & Encounter)	1,238,036	1,249,056	1,258,864	1,270,424	1,276,063	1,284,291	1,291,200	1,296,769	1,303,371	1,322,427	1,330,020	1,337,959	1,288,207
FFS Members	111,347	109,132	112,664	117,322	110,548	109,789	112,522	113,945	111,881	115,910	113,720	117,050	112,986
OHP Basic with Medicare	8,429	8,051	8,195	8,488	8,161	8,271	8,510	8,597	8,424	8,606	8,473	8,710	8,410
OHP Basic without Medicare	10,888	10,718	10,697	10,889	10,579	10,500	10,595	10,601	10,503	10,497	10,255	10,368	10,591
ACA	92,030	90,363	93,772	97,945	91,808	91,018	93,417	94,747	92,954	96,807	94,992	97,972	93,985
Encounter Members	1,126,689	1,139,924	1,146,200	1,153,102	1,165,515	1,174,502	1,178,678	1,182,824	1,191,490	1,206,517	1,216,300	1,220,909	1,175,221
OHP Basic with Medicare	84,715	86,139	86,570	87,412	88,084	89,468	90,661	92,068	93,206	94,346	95,446	96,256	90,364
OHP Basic without Medicare	67,983	68,260	68,173	68,310	68,509	68,469	68,580	68,801	68,956	69,022	69,064	68,981	68,592
ACA	973,991	985,525	991,457	997,380	1,008,922	1,016,565	1,019,437	1,021,955	1,029,328	1,043,149	1,051,790	1,055,672	1,016,264

Gross Cost Figures for Drugs	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	YTD Sum
Total Amount Paid (FFS & Encounter)	$97,567,578	$100,732,317	$103,179,492	$102,652,803	$98,866,801	$116,037,955	$106,332,953	$111,467,467	$113,308,637	$103,993,292	$116,906,068	$108,490,863	$1,279,536,227
Mental Health Carve-Out Drugs	$10,846,532	$11,004,341	$11,202,431	$11,267,660	$10,867,921	$12,312,593	$11,634,392	$12,131,859	$11,933,923	$11,110,104	$11,893,706	$11,165,717	$137,371,178
OHP Basic with Medicare	$8,509	$5,705	$2,848	$317	$11,314	$7,893	$11,471	$9,259	$10,001	$7,612	$3,774	$5,976	$84,680
OHP Basic without Medicare	$4,006,902	$4,051,571	$4,176,428	$4,088,497	$3,906,186	$4,429,201	$4,145,072	$4,340,706	$4,414,283	$3,994,456	$4,334,167	$4,142,537	$50,030,006
ACA	$6,749,467	$6,864,294	$6,935,596	$7,086,443	$6,860,346	$7,776,734	$7,390,154	$7,688,337	$7,431,446	$7,027,703	$7,486,978	$6,954,568	$86,252,065
FFS Physical Health Drugs	$4,524,991	$4,487,916	$4,568,492	$4,987,642	$4,506,737	$5,042,762	$5,259,902	$5,495,477	$5,205,948	$4,808,861	$5,617,932	$5,107,190	$59,613,851
OHP Basic with Medicare	$165,578	$171,115	$158,438	$187,735	$177,974	$206,926	$200,388	$210,055	$235,238	$209,713	$229,485	$197,390	$2,350,037
OHP Basic without Medicare	$1,201,423	$1,027,543	$1,116,720	$1,132,247	$989,978	$1,095,318	$1,162,627	$1,223,287	$1,192,739	$972,746	$1,218,045	$1,021,595	$13,354,269
ACA	$3,001,864	$3,125,176	$3,193,302	$3,519,646	$3,227,953	$3,624,956	$3,742,407	$3,910,375	$3,647,763	$3,473,499	$3,997,429	$3,735,689	$42,200,060
FFS Physician Administered Drugs	$1,435,900	$1,224,169	$1,074,441	$1,248,804	$1,674,370	$1,813,360	$1,366,563	$1,307,144	$1,650,727	$1,299,422	$1,151,861	$1,396,051	$16,642,813
OHP Basic with Medicare	$59,510	$153,016	$155,675	$165,886	$150,142	$142,481	$146,552	$103,159	$110,939	$180,889	$138,569	$163,587	$1,670,406
OHP Basic without Medicare	$584,257	$413,340	$232,799	$198,491	$523,118	$497,954	$258,208	$319,442	$565,692	$301,843	$103,641	$512,073	$4,510,858
ACA	$430,148	$364,983	$425,042	$402,708	$541,945	$614,379	$550,725	$519,456	$541,257	$389,835	$479,964	$384,359	$5,644,799
Encounter Physical Health Drugs	$63,546,085	$66,086,120	$68,053,611	$67,347,957	$64,528,143	$73,979,547	$69,198,239	$72,410,288	$71,999,713	$67,163,054	$75,697,235	$70,769,201	$830,779,193
OHP Basic with Medicare	$400,146	$447,118	$473,861	$427,250	$393,401	$443,092	$410,107	$426,618	$397,294	$356,217	$412,953	$378,967	$4,967,023
OHP Basic without Medicare	$15,462,625	$16,315,294	$16,372,701	$16,514,178	$16,148,892	$17,631,263	$17,063,434	$17,075,179	$17,299,326	$16,374,218	$17,927,063	$16,774,895	$200,959,068
ACA	$46,928,061	$48,565,122	$50,314,400	$49,541,281	$47,135,788	$54,872,117	$50,690,051	$53,876,306	$53,231,767	$49,220,947	$55,790,657	$52,006,452	$612,172,950
Encounter Physician Administered Drugs	$17,214,070	$17,929,770	$18,280,517	$17,800,741	$17,289,631	$22,889,692	$18,873,858	$20,122,698	$22,518,326	$19,611,851	$22,545,334	$20,052,704	$235,129,192
OHP Basic with Medicare	$1,037,778	$980,990	$905,449	$1,087,438	$880,280	$1,100,484	$970,582	$996,109	$1,164,351	$1,120,494	$1,023,117	$900,498	$12,167,570
OHP Basic without Medicare	$3,845,012	$4,267,556	$4,367,050	$3,854,782	$4,098,188	$5,600,190	$4,456,790	$5,749,556	$4,838,108	$4,529,706	$5,111,378	$4,315,757	$55,034,072
ACA	$12,159,419	$12,405,770	$12,803,305	$12,603,923	$12,049,321	$15,963,650	$13,277,830	$13,195,230	$16,163,987	$13,695,463	$16,052,192	$14,482,603	$164,852,692

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: April 20, 2023

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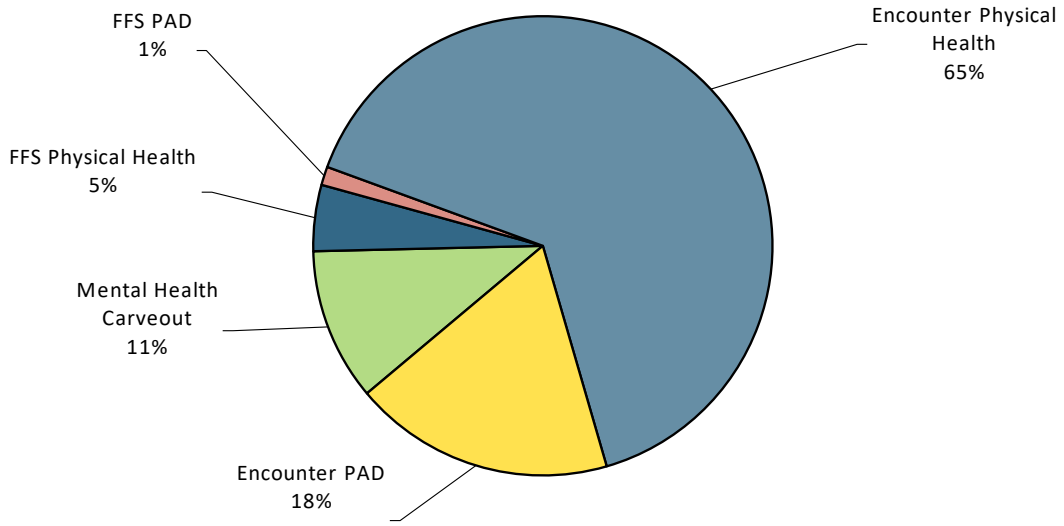
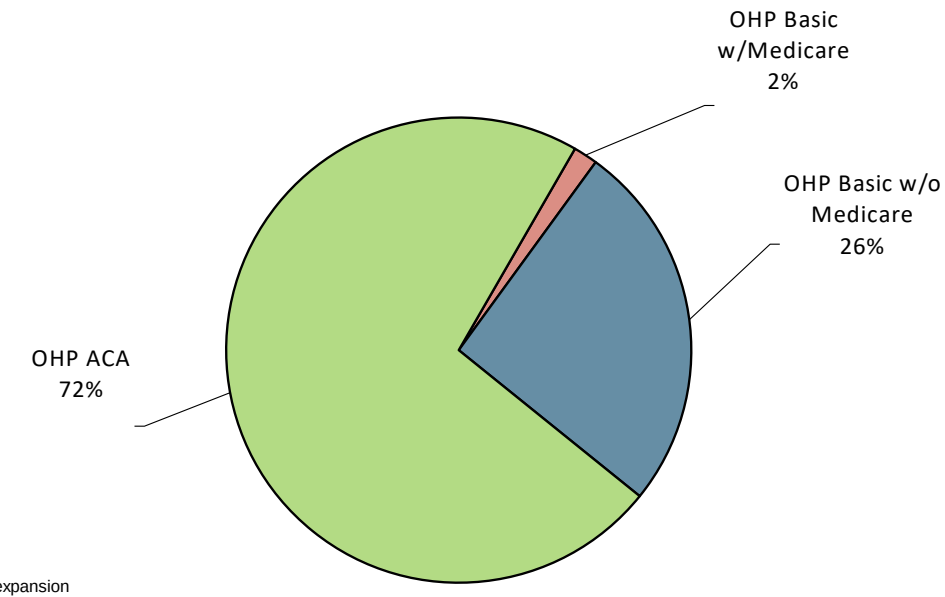
Pharmacy Utilization Summary Report: October 2021 - September 2022

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: April 20, 2023

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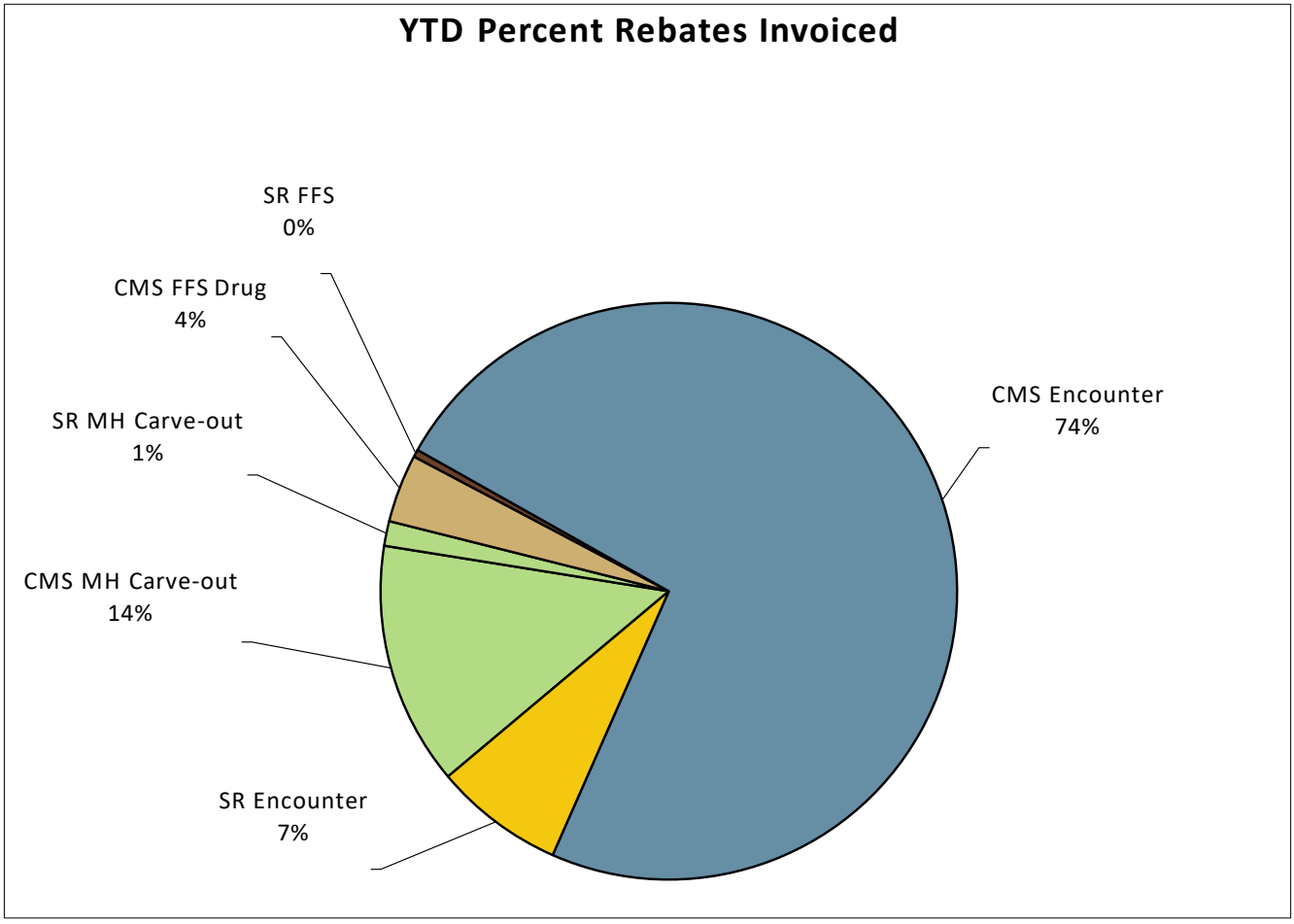
Pharmacy Utilization Summary Report: October 2021 - September 2022

Quarterly Rebates Invoiced	2021-Q4	2022-Q1	2022-Q2	2022-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$112,969,459	$120,549,011	$122,909,282	$153,620,091	$510,047,842
CMS MH Carve-out	$17,620,385	$17,110,132	$18,172,702	$16,653,224	$69,556,443
SR MH Carve-out	$1,795,141	$1,341,151	$1,717,026	$2,206,833	$7,060,151
CMS FFS Drug	$4,764,214	$4,805,957	$4,588,856	$5,343,007	$19,502,034
SR FFS	$553,362	$506,401	$511,077	$556,102	$2,126,942
CMS Encounter	$79,408,414	$88,415,263	$88,806,437	$118,006,598	$374,636,712
SR Encounter	$8,827,942	$8,370,109	$9,113,183	$10,854,326	$37,165,560

Quaterly Net Drug Costs	2021-Q4	2022-Q1	2022-Q2	2022-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$188,509,928	$197,008,548	$208,199,776	$175,770,133	$769,488,385
Mental Health Carve-Out Drugs	$13,637,777	$15,996,891	$15,810,446	$15,309,469	$60,754,584
FFS Phys Health + PAD	$11,998,334	$13,961,317	$15,185,828	$13,482,208	$54,627,688
Encounter Phys Health + PAD	$162,873,817	$167,050,340	$177,203,502	$146,978,456	$654,106,114



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

Last Updated: April 20, 2023

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Pharmacy Utilization Summary Report: October 2021 - September 2022

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$78.81	$80.65	$81.96	$80.80	$77.48	$90.35	$82.35	$85.96	$86.94	$78.64	$87.90	$81.09	$82.74
Mental Health Carve-Out Drugs	$8.76	$8.81	$8.90	$8.87	$8.52	$9.59	$9.01	$9.36	$9.16	$8.40	$8.94	$8.35	$8.89
FFS Physical Health Drugs	$40.64	$41.12	$40.55	$42.51	$40.77	$45.93	$46.75	$48.23	$46.53	$41.49	$49.40	$43.63	$43.96
FFS Physician Administered Drugs	$12.90	$11.22	$9.54	$10.64	$15.15	$16.52	$12.14	$11.47	$14.75	$11.21	$10.13	$11.93	$12.30
Encounter Physical Health Drugs	$56.40	$57.97	$59.37	$58.41	$55.36	$62.99	$58.71	$61.22	$60.43	$55.67	$62.24	$57.96	$58.89
Encounter Physician Administered Drugs	$15.28	$15.73	$15.95	$15.44	$14.83	$19.49	$16.01	$17.01	$18.90	$16.25	$18.54	$16.42	$16.65

Claim Counts	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Total Claim Count (FFS & Encounter)	1,096,840	1,097,603	1,110,758	1,125,464	1,050,206	1,201,373	1,147,555	1,182,939	1,174,102	1,105,437	1,201,473	1,139,812	1,136,130
Mental Health Carve-Out Drugs	183,238	185,502	188,476	190,963	179,890	204,411	193,148	199,466	197,731	189,762	206,390	194,299	192,773
FFS Physical Health Drugs	35,415	35,164	35,897	38,026	34,927	38,390	36,484	37,556	36,602	34,753	36,858	34,797	36,239
FFS Physician Administered Drugs	9,492	8,939	9,243	10,802	9,813	11,629	10,230	10,278	10,107	9,723	9,922	9,346	9,960
Encounter Physical Health Drugs	751,438	751,113	765,430	773,068	717,801	819,815	787,332	813,568	810,933	758,100	828,621	786,713	780,328
Encounter Physician Administered Drugs	117,257	116,885	111,712	112,605	107,775	127,128	120,361	122,071	118,729	113,099	119,682	114,657	116,830

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$88.95	$91.77	$92.89	$91.21	$94.14	$96.59	$92.66	$94.23	$96.51	$94.07	$97.30	$95.18	$93.79
Mental Health Carve-Out Drugs	$59.19	$59.32	$59.44	$59.00	$60.41	$60.23	$60.24	$60.82	$60.35	$58.55	$57.63	$57.47	$59.39
FFS Physical Health Drugs	$127.77	$127.63	$127.27	$131.16	$129.03	$131.36	$144.17	$146.33	$142.23	$138.37	$152.42	$146.77	$137.04
FFS Physician Administered Drugs	$151.27	$136.95	$116.24	$115.61	$170.63	$155.93	$133.58	$127.18	$163.33	$133.64	$116.09	$149.37	$139.15
Encounter Physical Health Drugs	$84.57	$87.98	$88.91	$87.12	$89.90	$90.24	$87.89	$89.00	$88.79	$88.59	$91.35	$89.96	$88.69
Encounter Physician Administered Drugs	$146.81	$153.40	$163.64	$158.08	$160.42	$180.05	$156.81	$164.84	$189.66	$173.40	$188.38	$174.89	$167.53

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.01	$22.59	$22.84	$23.10	$23.25	$23.57	$24.00	$24.02	$24.49	$24.44	$24.99	$25.02	$23.69
Mental Health Carve-Out Drugs	$16.23	$16.44	$16.35	$16.49	$16.42	$16.30	$16.64	$16.82	$17.06	$17.22	$17.57	$17.30	$16.74
FFS Physical Health Drugs	$78.01	$81.29	$81.05	$84.31	$84.17	$86.98	$97.23	$99.59	$99.68	$94.71	$103.46	$106.42	$91.41
Encounter Physical Health Drugs	$21.14	$21.80	$22.21	$22.25	$22.39	$22.75	$22.77	$22.66	$23.28	$23.41	$23.73	$23.74	$22.68

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$517.43	$547.40	$535.48	$538.46	$607.04	$648.11	$641.20	$654.25	$665.94	$670.46	$697.81	$643.94	$613.96
Mental Health Carve-Out Drugs	$964.54	$931.86	$950.74	$946.47	$965.71	$963.43	$962.47	$964.43	$1,020.82	$1,085.82	$1,115.90	$1,146.87	$1,001.59
FFS Physical Health Drugs	$319.51	$290.46	$272.83	$281.82	$315.12	$345.82	$372.77	$375.53	$350.00	$348.94	$400.59	$337.85	$334.27
Encounter Physical Health Drugs	$494.89	$533.62	$522.38	$525.94	$595.11	$637.00	$627.15	$641.63	$653.36	$656.00	$682.05	$625.26	$599.53

Generic Drug Use Percentage	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Generic Drug Use Percentage	88.0%	88.3%	87.9%	88.3%	89.3%	90.0%	90.2%	90.2%	90.5%	90.7%	90.8%	90.2%	89.5%
Mental Health Carve-Out Drugs	95.5%	95.3%	95.4%	95.4%	95.4%	95.4%	95.4%	95.4%	95.7%	96.1%	96.4%	96.4%	95.6%
FFS Physical Health Drugs	79.4%	77.8%	75.9%	76.3%	80.6%	82.9%	83.0%	83.1%	83.0%	82.8%	83.5%	82.6%	80.9%
Encounter Physical Health Drugs	86.6%	87.1%	86.7%	87.1%	88.2%	89.0%	89.2%	89.3%	89.6%	89.7%	89.7%	89.0%	88.4%

Preferred Drug Use Percentage	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Avg Monthly
Preferred Drug Use Percentage	89.88%	89.82%	89.76%	89.84%	89.81%	89.89%	89.88%	89.89%	89.82%	90.49%	90.42%	90.45%	90.0%
Mental Health Carve-Out Drugs	93.47%	93.34%	93.35%	93.31%	93.29%	93.31%	93.33%	93.31%	93.27%	93.24%	93.13%	93.13%	93.3%
FFS Physical Health Drugs	94.80%	94.96%	94.98%	94.52%	94.43%	94.54%	94.65%	94.80%	94.90%	95.65%	95.76%	95.68%	95.0%
Encounter Physical Health Drugs	88.78%	88.73%	88.65%	88.78%	88.73%	88.84%	88.85%	88.86%	88.79%	89.61%	89.54%	89.59%	89.0%

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: April 20, 2023

Drug Use Research & Management Program
DHS - Health Systems Division
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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2023

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA*	Antipsychotics, 2nd Gen	$5,310,994	12.0%	4,277	$1,242	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$4,183,668	9.5%	1,742	$2,402	Y
3	VRAYLAR*	Antipsychotics, 2nd Gen	$3,879,219	8.8%	3,208	$1,209	Y
4	REXULTI*	Antipsychotics, 2nd Gen	$2,332,005	5.3%	1,846	$1,263	V
5	ABILIFY MAINTENA	Antipsychotics, Parenteral	$2,239,350	5.1%	977	$2,292	Y
6	INVEGA TRINZA	Antipsychotics, Parenteral	$990,510	2.2%	136	$7,283	Y
7	ARISTADA	Antipsychotics, Parenteral	$856,384	1.9%	357	$2,399	Y
8	TRINTELLIX	Antidepressants	$850,345	1.9%	1,954	$435	V
9	SERTRALINE HCL	Antidepressants	$595,070	1.3%	61,129	$10	Y
10	CAPLYTA*	Antipsychotics, 2nd Gen	$592,347	1.3%	425	$1,394	V
11	BUPROPION XL	Antidepressants	$575,652	1.3%	45,212	$13	Y
12	DULOXETINE HCL	Antidepressants	$543,352	1.2%	38,138	$14	Y
13	FLUOXETINE HCL	Antidepressants	$512,170	1.2%	45,085	$11	Y
14	TRAZODONE HCL	Antidepressants	$506,627	1.1%	49,446	$10	
15	Epoetin Beta Esrd Use	Physican Administered Drug	$497,879	1.1%	60	$8,298	
16	LYBALVI*	Antipsychotics, 2nd Gen	$457,010	1.0%	346	$1,321	V
17	ESCITALOPRAM OXALATE	Antidepressants	$446,874	1.0%	44,357	$10	Y
18	ATOMOXETINE HCL*	ADHD Drugs	$379,902	0.9%	8,475	$45	Y
19	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$344,838	0.8%	27,775	$12	
20	LAMOTRIGINE	Antiepileptics, Outpatient	$327,389	0.7%	29,906	$11	Y
21	SPRAVATO*	Antidepressants	$321,949	0.7%	250	$1,288	V
22	Agalsidase Beta Injection	Physican Administered Drug	$294,122	0.7%	26	$11,312	
23	ARIPIPRAZOLE*	Antipsychotics, 2nd Gen	$273,704	0.6%	20,835	$13	Y
24	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$268,056	0.6%	259	$1,035	Y
25	LAMOTRIGINE ER	Antiepileptics, Outpatient	$265,247	0.6%	3,548	$75	V
26	BIKTARVY	HIV	$262,327	0.6%	106	$2,475	Y
27	BUPROPION XL	Antidepressants	$244,890	0.6%	1,349	$182	V
28	TRIKAFTA*	Cystic Fibrosis	$238,103	0.5%	30	$7,937	N
29	VENLAFAXINE HCL ER	Antidepressants	$237,133	0.5%	19,173	$12	Y
30	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$229,054	0.5%	20,876	$11	Y
31	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$227,819	0.5%	1	$227,819	
32	STELARA*	Targeted Immune Modulators	$216,090	0.5%	31	$6,971	N
33	CONCERTA*	ADHD Drugs	$211,398	0.5%	595	$355	Y
34	Elosulfase Alfa, Injection	Physican Administered Drug	$204,883	0.5%	12	$17,074	
35	CITALOPRAM HBR	Antidepressants	$180,225	0.4%	20,422	$9	Y
36	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$178,680	0.4%	17	$10,511	Y
37	MIRTAZAPINE	Antidepressants	$173,291	0.4%	12,571	$14	Y
38	PALIPERIDONE ER*	Antipsychotics, 2nd Gen	$173,105	0.4%	1,702	$102	V
39	OLANZAPINE*	Antipsychotics, 2nd Gen	$170,510	0.4%	13,398	$13	Y
40	AMITRIPTYLINE HCL*	Antidepressants	$169,999	0.4%	14,331	$12	Y
		Top 40 Aggregate:	**$30,962,171**		**494,383**	**$7,922**	
		All FFS Drugs Totals:	**$44,189,202**		**743,730**	**$730**	

*** 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: April 20, 2023

Drug Use Research & Management Program
DHS - Health Systems Division
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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - First Quarter 2023

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Epoetin Beta Esrd Use	Physican Administered Drug	$497,879	4.4%	60	$8,298	
2	Agalsidase Beta Injection	Physican Administered Drug	$294,122	2.6%	26	$11,312	
3	BIKTARVY	HIV	$262,327	2.3%	106	$2,475	Y
4	TRIKAFTA*	Cystic Fibrosis	$238,103	2.1%	30	$7,937	N
5	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$227,819	2.0%	1	$227,819	
6	STELARA*	Targeted Immune Modulators	$216,090	1.9%	31	$6,971	N
7	CONCERTA*	ADHD Drugs	$211,398	1.9%	595	$355	Y
8	Elosulfase Alfa, Injection	Physican Administered Drug	$204,883	1.8%	12	$17,074	
9	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$178,680	1.6%	17	$10,511	Y
10	VYVANSE*	ADHD Drugs	$168,585	1.5%	910	$185	Y
11	Iron Sucrose Injection	Physican Administered Drug	$143,984	1.3%	446	$323	
12	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$139,422	1.2%	3	$46,474	
13	LANTUS SOLOSTAR*	Diabetes, Insulins	$137,760	1.2%	440	$313	Y
14	IBRANCE*	Antineoplastics, Newer	$135,801	1.2%	9	$15,089	
15	HUMIRA(CF) PEN*	Targeted Immune Modulators	$132,941	1.2%	63	$2,110	Y
16	COSENTYX PEN (2 PENS)*	Targeted Immune Modulators	$126,581	1.1%	30	$4,219	Y
17	ELIQUIS	Anticoagulants, Oral and SQ	$118,755	1.1%	325	$365	Y
18	TRULICITY*	Diabetes, GLP-1 Receptor Agonistse and GIP the	$118,012	1.1%	231	$511	Y
19	EPIDIOLEX*	Antiepileptics, Outpatient	$116,286	1.0%	109	$1,067	N
20	Etonogestrel Implant System	Physican Administered Drug	$112,861	1.0%	165	$684	
21	SABRIL	Antiepileptics, Outpatient	$100,261	0.9%	3	$33,420	N
22	CHOLBAM*	Bile Therapy	$99,610	0.9%	1	$99,610	N
23	SPRYCEL	STC 30 - Antineoplastic	$99,609	0.9%	11	$9,055	
24	SUBLOCADE	Substance Use Disorders, Opioid & Alcohol	$98,830	0.9%	55	$1,797	Y
25	Inj Pembrolizumab	Physican Administered Drug	$92,977	0.8%	36	$2,583	
26	Aflibercept Injection	Physican Administered Drug	$92,747	0.8%	174	$533	
27	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$89,307	0.8%	6	$14,884	
28	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$89,142	0.8%	2,908	$31	Y
29	CREON	Pancreatic Enzymes	$87,591	0.8%	73	$1,200	Y
30	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$81,840	0.7%	1,327	$62	Y
31	Mirena, 52 Mg	Physican Administered Drug	$79,364	0.7%	120	$661	
32	VERZENIO*	Antineoplastics, Newer	$77,483	0.7%	8	$9,685	
33	KESIMPTA PEN*	Multiple Sclerosis	$73,465	0.7%	3	$24,488	N
34	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$72,084	0.6%	616	$117	
35	METYROSINE	STC 71 - Other Hypotensives	$69,850	0.6%	3	$23,283	
36	OZEMPIC*	Diabetes, GLP-1 Receptor Agonistse and GIP the	$65,526	0.6%	165	$397	N
37	PULMOZYME	Cystic Fibrosis	$61,877	0.6%	49	$1,263	Y
38	HUMIRA(CF)*	Targeted Immune Modulators	$61,760	0.6%	18	$3,431	Y
39	Injection, Nivolumab	Physican Administered Drug	$61,415	0.5%	15	$4,094	
40	LENALIDOMIDE	STC 30 - Antineoplastic	$60,501	0.5%	3	$20,167	
		Top 40 Aggregate:	**$5,397,527**		**9,203**	**$15,371**	
		All FFS Drugs Totals:	**$11,213,991**		**121,339**	**$752**	

*** Drug requires Prior Authorization**

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

Last updated: April 20, 2023

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
omidubicel-onlv	OMISIRGE
retifanlimab-dlwr	ZYNYZ

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy or 12 months, whichever is less.	**No**: Go to #4
4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	**No:** Go to #8
8. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	**No:** Go to #9
9. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria
10. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy (Updated 04~~3~~/06~~2~~7/2023)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA

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

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

Generic Name	Brand Name
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
tremlimumab	IMJUDO
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA

Generic Name	Brand Name
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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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
leniolisib	JOENJA
velmanase alfa-tycv	LAMZEDE

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
Alpelisib (VIJOICE)	PIK3CA-Related Overgrowth Spectrum (PROS) in those who require systemic therapy	≥ 2 yrs	Pediatric 2 to <18 yrs: • 50 mg once daily • May consider increase to 125 mg once daily if ≥6 years after 24 weeks of treatment • May gradually increase to 250 mg once daily once patient turns 18 Adult: • 250 mg once daily	Baseline Monitoring • Fasting BG, HbA1c Ongoing Monitoring • Fasting BG weekly x 2 weeks, then at least once every 4 weeks, then as clinically indicated • HbA1c every 3 months and as clinically indicated
Avacopan (TAVNEOS)	Severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with glucocorticoids.	≥18 yrs	30 mg (three 10 mg capsules) twice daily, with food	Baseline Monitoring • Liver function tests ALT, AST, ALP, and total bilirubin • Hepatitis B (HBsAg and anti-HBc) Ongoing Monitoring • Liver function tests every 4 wks for 6 months, then as clinically indicated
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH)	XLH ≥ 6 mo TIO	Pediatric <18 yrs: Initial (administered SC every 2 wks): XLH	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated

	FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	≥ 2 yrs	• <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 mg for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg) TIO: 0.5 mg/kg monthly initially (Max dose 2 mg/kg or 180mg every 2 wks)	• Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only: • Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Belumosudil (REZUROCK)	Treatment of chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy	≥ 12 yrs	200 mg orally once daily with food 200 mg twice daily when coadministered with strong CYP3A inducers or proton pump inhibitors	Baseline & Ongoing Monitoring • Total bilirubin, AST, ALT at least monthly • Pregnancy test (if childbearing potential)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 yrs	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 wks)	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

	cofactor deficiency (MoCD) Type A		Initial: 0.4mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 wks) Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥1 yr: 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 yrs	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests • Blood homocysteine levels-If homocysteine elevated, assess folate, vitamin B12, and vitamin B6
Leniolisib (JOENJA)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	≥ 12 years AND ≥ 45kg	70 mg administered orally twice daily approximately 12 hours apart	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 mo AND ≥0.39 m^2 BSA	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary and plasma oxalate levels	N/A	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months	N/A

			≥ 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 (Hgb <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hgb <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 yr	Initial: 1 mg/kg SC Max dose of 1.25 mg/kg every 3 wks for beta thalassemia Max dose of 1.75 mg/kg every 3 wks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 wks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 wks) • Hemoglobin level • Blood pressure
Maralixibat (LIVMARLI)	Cholestatic pruritis in patients with Alagille syndrome	≥ 3 mo	Initial: 190 mcg/kg once daily, 30 min before first meal of day Goal: 380 mcg/kg once daily after 1 week on initial dose, as tolerated	Baseline/Ongoing Monitoring • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Mitapivat (PYRUKYND)	Hemolytic anemia in adults with pyruvate kinase (PK) deficiency.	≥ 18 yr	Initial: 5 mg twice daily Titration: If Hb less than normal range or patient required transfusion in previous 8 weeks, then after 4 weeks increase to 20 mg twice daily, and after another 4 weeks increase to 50 mg twice daily. Max dose: 50 mg twice daily Discontinuation should include down-titration.	Baseline/Ongoing Monitoring • Hgb, transfusion requirement

Odevixibat (BYLVAY)	Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: may not be effective in PFIC type 2 in patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)	≥ 3 mo	Initial: 40 mcg/kg once daily with morning meal Titration: After 3 months of initial dose, 40 mcg/kg increments Max dose: 120 mcg/kg once daily; not to exceed 6 mg	<u>Baseline/Ongoing Monitoring</u> • Liver function tests (ALT, AST, total bilirubin and direct bilirubin) • Fat soluble vitamins (A, D, E, K); INR used as surrogate for Vitamin K
Olipudase alfa-rpcp (XENPOZYME)	Non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD)	N/A	Initial: Age based dose escalation table per Package insert Maintenance: 3 mg/kg via IV infusion every 2 weeks Weight: • If BMI ≤ 30, use actual body weight • If BMI > 30, use adjusted body weight Adjusted body weight (kg) = (actual height in M)^2 x 30	<u>Baseline Monitoring</u> • Liver function tests (ALT, AST) within 1 month • Pregnancy test (if childbearing potential) <u>Ongoing Monitoring</u> • Liver function tests (ALT, AST) within 72 hours of infusions during dose escalation, then during routine clinical management once at maintenance dose
Plasminogen, human-tvmh (RYPLAZIM)	Treatment of patients with plasminogen deficiency type 1 (hypoplasmino-genemia)	N/A	6.6 mg/kg body weight given IV every 2 to 4 days	<u>Baseline Monitoring</u> • Plasminogen activity level (allow 7 day washout if receiving with fresh frozen plasma) • CBC (bleeding) <u>Ongoing Monitoring</u> • Trough Plasminogen activity level 72 hours after initial dose and every 12 wks with ongoing therapy • CBC (bleeding)
Sodium thiosulfate (PEDMARK)	Decrease ototoxicity associated with cisplatin infusions lasting ≤ 6 hours. Not approved for use with longer infusions.	≥ 1 mo to ≤18 yr	< 5 kg: 10 g/m^2 5-10 kg: 15 g/m^2 >10 kg: 20 g/m^2	<u>Baseline Monitoring</u> • Serum potassium and sodium
Sutimlimab-jome (ENJAYMO)	Decrease need for RBC transfusion due to hemolysis in cold agglutinin disease (CAD)	≥ 18 yr	Dosed IV infusion weekly for two weeks, then every two weeks thereafter. **39 to <75 kg** 6500 mg	<u>Baseline Monitoring</u> • Vaccination against encapsulated bacteria (*Neisseria meningititides* (any serogroup)*, Streptococcus pneumonia,* and *Haemophilus influenza*) at least prior to treatment or as soon as possible if urgent therapy needed

			≥75 kg 7500 mg	
Trientine tetrahydrochloride (CUVRIOR)	Stable Wilson's disease who are de-coppered and tolerant to penicillamine	≥ 18 yr	Total daily dose in transition from penicillamine per table in package insert.	Baseline/Ongoing Monitoring • Serum NCC levels at baseline, 3 months, then roughly every 6 months serum levels or 6 to 12 months with urinary copper excretion
Velmanase alfa-tycv (LAMZEDE)	Treatment of non-central nervous system manifestations of alpha-mannosidosis	N/A	1 mg/kg (actual body weight) once weekly by IV infusion	Baseline and ongoing monitoring • Pregnancy test (if childbearing potential)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase, AST = aspartate aminotransferase; BG = blood glucose; BSA = body surface area; CBC = complete blood count; CrCL = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycalated hemoglobin; Hgb = hemoglobin; INR = international normalized ratio; IV = intravenous; mo = months; NCC = non-ceruloplasmin copper; RBC = red blood cells; SC = subcutaneously; wks = weeks; yrs = years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6

Approval Criteria		
6. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
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: 6/23; 2/23; 12/22; 6/22; 4/22; 12/21; 10/21; 6/21; 2/21; 8/20; 6/20; 2/20
Implementation: TBD; 4/1/23; 1/1/23; 7/1/22; 5/1/22; 1/1/2022; 7/1/2021; 3/1/21; 11/1/20; 9/1/20; 7/1/20

ProDUR Report for January through March 2023
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	10	6	0	4	0.0%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	1,932	487	0	1,443	1.2%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	8,285	2,460	0	5,816	5.3%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	98,848	19,357	104	79,382	63.5%	**19.6%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	34,242	9,512	4	24,671	22.0%	**N/A**
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	807	160	0	645	0.5%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	8	8	0	0	0.0%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	715	226	0	489	0.4%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	449	161	0	286	0.3%	**N/A**
PA (Drug/Age Precaution)	Products containing Codeine or Tramadol being billed and patient is less than 18 years of age	Set alert/Pay claim	1	0	0	1	0.0%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	21	18	0	3	0.0%	**85.7%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	10,181	2,974	5	7,186	6.5%	**N/A**
		Totals	**155,499**					

ProDUR Report for January through March 2023
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	8,345	1,458	6,886	84,984	9.8%	17.5%
ER	Prozac (Fluoxetine)	5,763	1,045	4,718	60,481	9.5%	18.1%
ER	Lexapro (Escitalopram)	5,747	1,078	4,669	63,731	9.0%	18.8%
ER	Celexa (Citalopram)	2,194	371	1,823	27,358	8.0%	16.9%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	7,697	1,254	6,443	82,861	9.3%	16.3%
ER	Trazodone	7,019	1,288	5,731	66,000	10.6%	18.4%
ER	Cymbalta (Duloxetine)	5,120	966	4,154	51,252	10.0%	18.9%
ER	Effexor (Venlafaxine)	2,929	535	2,393	31,854	9.1%	18.3%
ER	Remeron (Mirtazapine)	2,041	302	1,739	17,222	11.8%	14.8%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	4,860	1,167	3,692	35,241	13.7%	24.0%
ER	Abilify (Aripiprazole)	4,044	668	3,376	31,681	12.7%	16.5%
ER	Zyprexa (Olanzapine)	2,845	664	2,181	21,358	13.3%	23.3%
ER	Risperdal (Risperidone)	2,084	496	1,587	14,581	14.3%	23.8%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	3,680	582	3,098	37,345	9.8%	15.8%
ER	Lorazepam	311	77	234	12,593	2.4%	24.8%
ER	Alprazolam	192	43	149	8,087	2.3%	22.4%
ER	Diazepam	125	39	86	4,502	2.7%	31.2%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	6,589	1,264	5,325	49,141	13.4%	19.2%
ER	Intuniv (Guanfacine ER)	1,815	282	1,533	13,722	13.2%	15.5%
ER	Suboxone (Buprenorphine/Naloxone)	129	40	89	2,089	6.2%	31.0%

ProDUR Report for January through March 2023

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	January	4,226	112	260	749	7	2,831	94	0	173
ER	February	4,377	143	239	749	3	3,017	61	2	163
ER	March	4,312	158	274	675	2	2,996	52	0	155
	Total =	**12,915**	**413**	**773**	**2,173**	**12**	**8,844**	**207**	**2**	**491**
	Percentage of total overrides =		**3.2%**	**6.0%**	**16.8%**	**0.1%**	**68.5%**	**1.6%**	**0.0%**	**3.8%**

ProDUR Report for January through March 2023			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
January	DD	20	$2,546.19
	ER	17	$5,532.40
	ID	8	$1,196.93
	TD	1	$75.48
		January Savings =	**$9,351.00**
February	DD	19	$3,338.19
	ER	39	$6,472.69
	HD	1	$2.92
	ID	11	$1,558.77
	TD	4	$4,646.05
		February Savings =	**$16,018.62**
March	DC	2	$895.98
	DD	25	$7,398.22
	ER	94	$20,779.33
	ID	23	$7,425.74
	LR	2	$456.63
	MX	1	$115.91
	TD	3	$427.67
		March Savings =	**$37,499.48**
Total 1Q2023 Savings =			**$62,869.10**

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	18	13		
		Unique Patients Identified	18	13		
		Total Faxes Successfully Sent	12	8		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	3	5		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$1,849	$4,061		
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	119	103	6	
		Unique Patients Identified	120	103	7	
		Total Faxes Successfully Sent	76	83	5	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	64	44	2	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$44,527	$13,548	$435	
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	109	56		
		Unique Patients Identified	110	56		
		Total Faxes Successfully Sent	69	35		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	40	16		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$4,854	$1,283		

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	2	9		
		Total Faxes Successfully Sent	1	5		
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent		3		
		Safety Monitoring Profiles Identified	2	1		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$0	$130		

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	1064	776		
		High risk patients identified	6	9		
		Prescribers successfully notified	6	8		
		Patients with change in antipsychotic drug in following 90 days		1		
		Patients with continued antipsychotic therapy in the following 90 days	5	6		
		Patients with discontinuation of antipsychotic therapy in the following 90 days	1			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	55	54	6	
		Total prescribers identified	55	54	6	
		Prescribers successfully notified	53	54		
		Patients with claims for the same antipsychotic within the next 90 days	31	24		
		Patients with claims for a different antipsychotic within the next 90 days	2	2		

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	80	57		
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	56	20		
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	207	169		
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	39	28		
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	3	17		
		Letters Sent To Providers		1		
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	1	9		
		Letters Sent To Providers	1	7		
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	8	10		
		Letters Sent To Providers	4	8		
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	31	10		
		Letters Sent To Providers	5	1		
	Lock-In	RetroDUR Profiles Reviewed		10		
		Locked In		0		
	Polypharmacy	RetroDUR Profiles Reviewed	18	1		
		Letters Sent To Providers	1			

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	16	16	1	
		Total prescribers identified	15	16	1	
		Prescribers successfully notified	15	12		
		Patients with paid claims within next 60 days	12	8		
		Patients with denied claim within next 60 days	13	7		

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Retro-DUR Intervention History by Quarter FFY 2022 - 2023

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	83	92	19	
		Total prescribers identified	82	91	19	
		Prescribers successfully notified	61	91		
		Patients with discontinuation of therapy within next 90 days	19	33	19	
		Patients with new prescription for naloxone within next 90 days	6	4		
		Average number of sedative drugs dispensed within next 90 days	22	16	0	
		Average number of sedative prescribers writing prescriptions in next 90 days	22	16	0	
	Oncology Denials	Total patients identified	1	2		
		Total prescribers identified	1	2		
		Prescribers successfully notified	1	2		
		Patients with claims for the same drug within the next 90 days		1		
		Patients with claims for any oncology agent within the next 90 days		1		
	TCAs in Children	TCA Denials in Children	26	21	3	
		Total patients identified	12	10	2	
		Total prescribers identified	12	10	2	
		Prescribers successfully notified	8	6		
		Patients with claims for a TCA within the next 90 days	3	2		

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November 2022 Volume 12 Issue 9

Hormone Replacement Therapy – A Focus on the Benefits and Risks of Estrogen

Kathy Sentena, Pharm.D., Oregon State University Drug Use Research and Management Group

Hormone replace therapy (HRT) is used by over 6 million women to manage symptoms of menopause.[1] Estrogen, used with or without progestin products, comprise most HRT regimens. Estrogen is FDA-approved for the treatment of menopausal conditions such as vasomotor symptoms and vaginal atrophic changes, and prevention of osteoporosis.[2] Estrogen is also used off-label for gender dysphoria disorder and palliative care in metastatic breast and prostate cancer.[3] Evidence has demonstrated benefits of HRT beyond symptom management; however, risks associated with HRT have also been identified. This newsletter will focus on the most recent findings of the benefits and risks of HRT, and provide reviews of two new estrogen products.

Background

Decreased estrogen levels with corresponding cessation of menstrual cycle and vasomotor, musculoskeletal, urogenital and psychological symptoms are associated with menopause.[4] These symptoms can be associated with decreased quality of life affecting families and work environments.[2] Approximately 60% to 80% of women experience menopausal symptoms, 20% of them are considered severe. Reported prevalence varies by ethnicity, with a higher incidence in Black and Hispanic women.[5] Menopause has also been identified as an independent risk factor for cardiovascular disease (CVD).[2]

Treatment recommendations for menopausal symptoms include the use of lubricants and gels as well as lifestyle modifications (e.g., weight loss, smoking cessation). Estrogen products are considered the most effective treatment for vasomotor symptoms and should be considered in women who need additional treatment and do not have contraindications. In women with an intact uterus,oral estrogen is given in combination with progestins to avoid hyperplasia or carcinoma.[5] Estrogen is available as the following dosage formulations: oral, vaginal, intranasal, transdermal or subcutaneous implant. Estrogen derivatives include estradiol, estradiol valerate synthetic conjugated estrogens, ethinyl estradiol, or conjugated equine estrogen.

Evidence for the Use of HRT

There is substantial evidence for the use of HRT for the management of menopausal symptoms; however evidence for the long-term benefits and risks of HRT for other indications has been mixed. Findings from the Women's Health Initiative (WHI) found HRT prevented fractures and colon cancer, but noted an increased risk of cardiovascular (CV) events and breast cancer.[6] Mixed evidence has also suggested the use of HRT in older women for prevention of CV disease, osteoporosis and cognitive decline. Observational studies of HRT have demonstrated a reduced risk of coronary heart disease (CHD); however, findings from randomized controlled trials (RCTs) failed to demonstrate CHD benefits.[2] The United States Preventative Services Task Force (USPSTF) recommends against the use of HRT for the primary prevention of chronic conditions.[7]

New Evidence

Two high quality systematic reviews, from the Agency for Healthcare Research and Quality (AHRQ) and Cochrane Database for Systematic Reviews, evaluated the benefits of HRT.[2,8] Hormone therapy for the primary prevention of chronic conditions in postmenopausal women was the focus of the AHRQ review. Estrogen use alone was found to reduce the risk of diabetes and fractures, while combination estrogen and progestin therapy was found to decrease the risk of colorectal cancers, diabetes and fractures (Table 1).[2] Evidence demonstrated estrogen use was not associated with developing or preventing dementia. Long-term (at least 1 year) HRT resulted in reductions in the risk of fracture for perimenopausal and menopausal women.[8]

Table 1. Benefits of HRT*[2]

Outcome	Results
Estrogen Monotherapy	
Diabetes	137 fewer cases per 10,000
Fractures	382 fewer cases per 10,000
Estrogen and Progestin Therapy	
Colorectal cancer	33 fewer cases per 10,000
Diabetes	77 fewer cases per 10,000
Fractures	222 fewer cases per 10,000

** Compared to placebo or no treatment*

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) recommends the use of estrogens for management of vasomotor symptoms based on low- to moderate-quality evidence.[4] Counseling the patient on the short and longer-term benefits and risks should be a part of the discussion with women considering HRT. The use of vaginal estrogens are also recommended for women with urogenital atrophy, in patients taking systemic HRT still experiencing symptoms, or in those in which systemic therapy is contraindicated.[4]

Risks of HRT

Some of the harms associated with the use of HRT is founded on substantial evidence while others are less clearly

elucidated. The use of HRT has been shown to increase the risk of breast cancer when used as estrogen alone or in combination therapy with progestins. Compared to placebo, there is an increased risk of breast cancer with combination therapy with a relative risk [RR] of 1.27 (95% confidence interval [CI], 1.03 to 1.56) and an increased risk of invasive breast cancer with an incidence of 52 more cases than placebo for every 10,000 women treated.[2,8] Guidelines advise of an increased risk of breast cancer with all HRT preparations except for vaginal estrogens.[4] The increased risk persists for more than 10 years after HRT is discontinued.[4]

There is also a notable increased risk of venous thromboembolism (VTE) with oral HRT, which can present early in treatment and increases with age.[4] A retrospective review found an increased risk with oral estrogens (e.g. conjugated estrogens and estradiol used alone and in combination with progestins), compared to no exposure, OR 1.58 (95% CI, 1.52 to 1.64).[9] The risk of VTE is not significantly increased with the use of transdermal products. If HRT is discontinued the increased risk of VTE is eliminated. Guidelines recommend that for women who are at increased risk of VTE or who have a body mass index greater than 30 kg/m^2 should consider transdermal HRT instead of oral therapy.[4]

Other harms associated with HRT include: gallbladder disease, stroke, and urinary incontinence.[2,8] The evidence on an increased risk of stroke with the use of HRT is low to very low-quality, preventing strong conclusions. There is no additional CV risk noted with HRT use in women under the age of 60 years and no evidence of an increased risk of CV mortality. Recently, there has also been an association of an increased risk of ovarian cancer with the use of HRT.[10]

While the risks with estrogen therapy appear to be dose related, there is insufficient evidence to direct optimal doses or suggest lower doses are without risk. Oral estrogens should be avoided in women who are at high risk of CV disease, thromboembolic disease or certain cancers (e.g., breast, uterine).[8]

New Estrogen Formulations

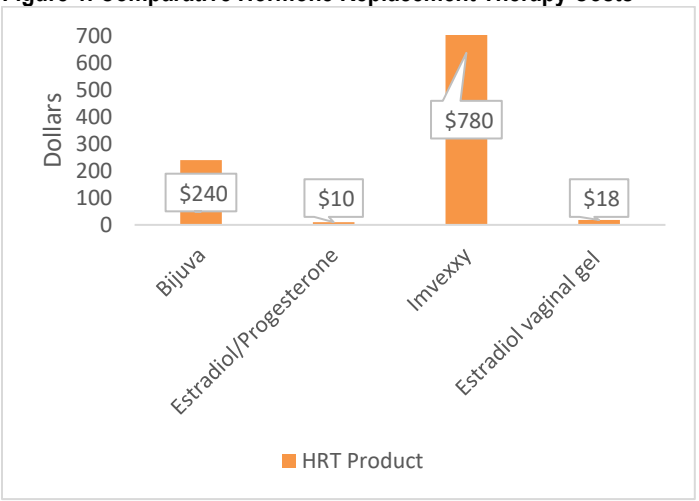
Bijuva®: In 2018 a new drug approval was granted for the estradiol/progesterone 0.5 mg/100 mg and 1 mg/100 mg combination oral capsule indicated for women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.[11] Combination estradiol/progesterone was shown to reduce moderate to severe vasomotor symptoms, frequency and severity, more than placebo in one, 12-week, randomized study (n=726). Women included in the study had at least 50 moderate to severe vasomotor symptoms per week and severity score was 2.55 at baseline. At 12 weeks, reduction in mean weekly *frequency* of symptoms were reported as clinically meaningful with a difference from placebo in the estradiol/progesterone arm of -16.58 episodes; p<0.001.[11] The *severity* of weekly moderate to severe vasomotor symptoms was reduced with estradiol/progesterone by -0.57 (p<0.001) compared to placebo at week 12. Four cases of breast cancer were diagnosed over the year-long safety study, 2 in patients treated with estradiol/progesterone 0.5 mg/100 mg, 2 in the estradiol/progesterone 1 mg/100 mg group and none in the placebo group.

Imvexxy®: Estradiol vaginal inserts 4 mcg and 10 mcg were approved in 2018 for the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.[12] Evidence for approval was from one, 12-week, double-blind, placebo-controlled, study of 574 women who were postmenopausal. For moderate to severe symptoms of dyspareunia, associated with postmenopausal vulvar and vaginal atrophy, improvements at 12 weeks compared to baseline were the following; estradiol 4 mcg, estradiol 12 mcg and placebo, -1.52 (p = 0.0149 compared to placebo), -1.69 (p<0.0001 compared to placebo) and -1.28, respectively.[11,12]

As with other estrogen products both Bijuva® and Imvexxy®, have a black box warning for an increased risk of stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction.[12] There is also evidence of increased risk of invasive breast cancer and probable increased risk of dementia in postmenopausal women, 65 years and older.

Limitations to the evidence for both new products include no direct comparisons to currently available treatment options and only short-term data on efficacy and safety findings. Current evidence supports utilization of more cost-effective generic options over the new formulations (Figure 1).

Figure 1. Comparative Hormone Replacement Therapy Costs*



* Costs are for a 30-day supply of selected therapies based on Meyers and Stauffers Average Actual Acquisition Cost (AAAC) Accessed 11.4.22.

Conclusion

Estrogens are an integral component of HRT. The demonstrated benefits of estrogen on menopausal symptoms are supported by high quality evidence; however, there are important potential risks of therapy that should be discussed with those considering HRT.

Peer reviewed by: Tracy Klein, PhD, ARNP, FAANP, FRE, FAAN, Assistant Director, Center for Cannabis Policy, Research and Outreach, Associate Professor, College of Nursing, Washington State University Vancouver

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Pharmacological Prevention and Treatment of Monkeypox

Sara Fletcher, PharmD, MPH, BCPS, Oregon State University Drug Use Research and Management Group

Introduction

Human monkeypox infection (hMPXV) is caused by the monkeypox virus. This double-stranded DNA virus is categorized in the same *Orthopoxvirus* genus as the smallpox (Variola) virus.[1] Pox viruses all elicit cross-reactive humoral and cellular immune responses.[2] Monkeypox was first identified in the 1950's in macaque research monkeys. In 1970, human cases were identified in the Democratic Republic of Congo.[2] There are two genetic clades for hMPXV based on location origin, with a historic fatality rate of 10.6% for clade I and 3.6% for the less virulent clade II.[2]

Spread of clade II hMPXV outside of endemic African nations was identified in early 2022. The World Health Organization declared the global spread of hMPXV a public health emergency of international concern in July 2022. Spread is generally through to close or intimate skin-to-skin contact (including sex), contact with respiratory secretions, and contact with objects, fabrics, and surfaces used by someone with monkeypox.[3] Most cases have occurred in gay, bisexual, and other men or have sex with men, though any patient with exposure, regardless of sexual or gender identity, is at risk of acquisition.[4]

The incubation period of hMPXV ranges from 5 to 21 days, while the disease itself can remain symptomatic for 2 to 4 weeks. The key sign is rash which may be painful or itchy, though other generalized viral symptoms (e.g. fever, chills, swollen lymph nodes) may also occur. Children and those with underlying immune deficiencies may have more severe cases with worse outcomes.[5] Over 235 total cases (confirmed and presumptive) have been identified in Oregon as of Oct 26th, with two pediatric patients.[6]

Vaccination

It is estimated that the smallpox vaccine may provide up to 85% efficacy against hMPXV infection, though this is based on historical data from the 1980s.[1] It is unknown if vaccine efficacy may wane over time for those vaccinated prior to smallpox eradication, and the current hMPXV may have mutations affecting its susceptibility to preexisting immunity. Human studies of vaccine efficacy for hMPXV are lacking.

After exposure to hMPXV, the Centers for Disease Control and Prevention (CDC) recommends vaccination within 4 days to prevent disease. Vaccination between days 4 to14 may not prevent disease, but may reduce the symptom severity.[4]

JYNNEOS (modified vaccinia Ankara vaccine) was Food and Drug Administration (FDA) approved in 2019 for prevention of smallpox and hMPXV in adults 18 years and older determined to be at high risk.[7] The vaccine was originally approved as a subcutaneous (SC) injection. In August 2022, JYNNEOS was granted an emergency use authorization (EUA) for intradermal injection of those at high-risk for hMPXV infection. Intradermal administration allows for a smaller injection volume and effectively increased the amount of vaccine doses five-fold. This was based on existing data showing intradermal administration at one-fifth the SC dose elicited a similar immune response. Additionally, the EUA allows for subcutaneous administration for those under 18 years of age. Two doses should be given 4 weeks apart. Data are not available to show effectiveness after a single dose. A patient is considered vaccinated 2 weeks after the second vaccine dose.[4,8] Severe adverse events are rare. Common side effects are primarily associated with local injection site pain and discomfort.[9] To obtain the JYNNEOS vaccine, Oregon Health Authority has guidance on eligibility[6] and access to a vaccine locator.[10]

ACAM2000 live virus vaccine is FDA approved for prevention of smallpox for those at high risk of infection.[11] An Expanded Access Investigational New Drug (EA-IND) Application allows for its use for the prevention of hMPXV in those 1 year and older.[4] It is given percutaneously via a bifurcated needle as a single dose with peak immunity at ~4 weeks. Significant adverse events of myopericarditis/pericarditis and vaccinia virus transmission are possible.[4,11] This second-generation smallpox vaccine will leave a scar similar to the now discontinued, first generation "DRYVAX" vaccine used historically in smallpox eradication efforts. ACAM2000 has a number of contraindications which should be carefully assessed. These include patients living with HIV (regardless of immune status) and atopic dermatitis.[11] Currently ACAM2000 is part of the Strategic National Stockpile (SNS) and only available to military personnel and laboratory workers who work with certain pox viruses, or through expanded access (compassionate use).[4]

Treatment

Pharmacologic options are limited, as no agents are currently approved specifically for hMPXV treatment. Herbal supplements are not recommended. The CDC recommends that those with high-risk disease manifestations or with

higher risk for severe disease should be considered for treatment (Table 1).[4]

Table 1. Patient Characteristics for Prioritized Antiviral Treatment[4]

Clinical Manifestations	• Severe disease (e.g. infected or bleeding lesions, hospitalization, periorbital infections, hemorrhagic disease) • Lesion anatomic location at risk of scarring or strictures (e.g. pharynx, penile foreskin, vulva, rectum)
Risk for Severe Disease	• Severely immunocompromised conditions • Pediatrics, especially less than 8 years of age • Pregnant or breastfeeding • Preexisting condition affecting skin integrity (e.g. atopic dermatitis, severe acne)

Tecovirimat (TPOXX) is Food and Drug Administration approved for use in human smallpox in adults and children weighing at least 3 kg.[12] Given the unique circumstances and ethics of studying a treatment for the eradicated disease of smallpox, tecovirimat efficacy was assessed using primate (monkeypox) and rabbit (rabbitpox) models in line with the FDA Animal Efficacy Rule.[13] Pharmacokinetics and safety were separately tested in over 400 healthy adult volunteers. Headache was the most common adverse event. Pediatric dosing was based on pharmacokinetic simulations to provide comparable exposure to that of adults.[12] Use in hMPXV is considered experimental and current evidence in humans is limited to sources such as case reports and retrospective cohorts.[14-16] Initial data from patients treated with tecovirimat during this hMPXV outbreak show few adverse events.[16] This medication is currently available through the national stockpile and prepositioned supplies. Providers requesting TPOXX must obtain it through the OHA.[17]

Vaccinia Immune Globulin Intravenous (VIGIV) is licensed by the FDA for complications due to vaccinia (smallpox) vaccination.[18] Post-exposure prophylaxis for hMPXV with VIGIV may be considered in those at risk of severe disease where vaccination is contraindicated, such as severe immunodeficiency in T-cell function.[4] Data are not available for effectiveness of treatment of hMPXV. Use may be considered in severe cases after weighing risk and benefit. Adverse events are similar to other IVIG products.[18]

Two other antivirals, cidofovir and brincidofovir, have *in vitro* and animal data to show effectiveness against orthopoxviruses, but not human data specific to hMPXV. Cidofovir is commercially available for treatment of cytomegalovirus retinitis, though severe renal toxicity is a known adverse effect of this product. Additionally, an expanded access protocol allows for use from the SNS. Brincidofovir, FDA approved for treatment of smallpox, may have a preferred safety profile over cidofovir, but does not yet have an EA-IND for use and is not available from the SNS.[4]

- Pharmacologic prevention and treatment options for hMPXV are derived from therapies for smallpox.
- Therapeutic recommendations may change as effectiveness and safety data become available from use in humans for hMPXV.

Conclusion

The hMPXV outbreak is evolving. Current pharmacologic treatment recommendations include prevention of disease through vaccination of people at high risk of exposure, and post-exposure prophylaxis immediately after known exposure. Antiviral treatment should be considered in patients exhibiting certain significant disease manifestations, as well at patients at higher risk of developing severe disease. Evidence supporting vaccines and antiviral treatments are primarily based on historic smallpox data, animal models, and pharmacokinetic data. Recommendations may evolve over time as real-world data for use of these agents in hMPXV become available through case reports and randomized trials.

Peer Reviewed By: Jennifer J Stanislaw, PharmD, BCACP, Assistant Professor, Oregon State University and Holly Villamagna, MD, Assistant Professor, Infectious Diseases, OHSU

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Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Benefit for Children and Adolescents

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The Medicaid Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit was introduced as a part of the Social Security Act Amendments of 1967.[1] The EPSDT benefit ensures children and adolescents under 21 years of age enrolled in Medicaid receive appropriate preventative, dental, mental health, and developmental specialty services, so that health problems are averted or diagnosed and treated as early as possible.[1] The EPSDT standard requires states to cover all medically necessary and medically appropriate treatment for children and adolescents on Medicaid, including medications, regardless of what services states provide to adults.[1] As the Oregon Pharmacy and Therapeutics (P & T) Committee reviews different medication classes, prior authorization (PA) criteria will be updated to support individualized review of medications based on medically appropriate and medically necessary use for members from birth up to their 21st birthday. This newsletter will summarize recent PA updates to reflect changes to the EPSDT benefit in qualifying Oregon Medicaid recipients

EPSDT in Oregon

Oregon is the only state that had a federal waiver approved by Centers for Medicare and Medicaid Services (CMS) to use a different approach to provide EPSDT services. This waiver allowed the state to restrict coverage of treatment services identified during an EPSDT screening for individuals from 1 year up to their 21st birthday to the extent that such services were not consistent with the Prioritized List of Health Services on lines 473 to 662 as determined by the Health Evidence Review Commission (HERC). In Oregon Medicaid, the longstanding EPSDT waiver will not be renewed and the Federal EPSDT benefit requirements will go into effect on 1/1/2023. Some medical treatments that Oregon has historically categorized as not available, will be available if they are medically necessary and medically appropriate for the individual OHP member under the age of 21 years. Under EPSDT, the Prioritized List is a guidance tool for assessment of coverage. Medically appropriate and medically necessary services are defined in Oregon Administrative Rule (OAR) 410-120-000.

Medications for Non-Funded Conditions

Non-preferred medications and medications reviewed by the Oregon P & T Committee for Oregon Health Plan (OHP) non-funded conditions require PA in adults. A case-by-case review for children and adolescents covered under the EPSDT program will be implemented 1/1/23. In the absence of more specific criteria already approved by the P & T Committee, standard definitons for medically appropriate and necessary use will include:

- FDA-approved or compendia-supported (such as Micromedex®) indication;
- Trial and failure, contradindication, or intolerance to at least 2 preferrred products (when available in the class); and The provider must submit a PA request and provide documentation that the condition for which the therapy is requested is of sufficient severity that it impacts the patienthealth (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc).

Allergic Rhinitis

For adults, allergic rhinitis is a non-funded condition unless a comorbidity, such as asthma or sleep apnea is present. At the August 2022 meeting, the P & T committee approved a recommendation to remove PA for preferred intranasal allergy products in children and adolescents under the age of 21 years per the EPSDT Medicaid benefit. For non-preferred drugs, the provider must submit a PA request and provide documentation that the patient's allergic rhinitis is of sufficient severity that it impacts the patient's health. The PA approval is dependent on the patient's failure to achieve benefit with (or have contraindications or intolerance to) the preferred intranasal allergy inhaler, fluticasone.

Medicaid Fee-For-Service: Intranasal Allergy Inhalers
Preferred Drug: Fluticasone
Non-Preferred Drugs (Require PA): Azelastine, Azelastine/Fluticasone Beclomethasone, Ciclesonide, Flunisolide, Mometasone, Olopatadine, Triamcinolone

Topical Agents for Inflammatory Skin Conditions

Clinical PA criteria for all drugs used to manage inflammatory skin conditions were updated in 2022 to reflect 2022 HERC guidance described in Guideline Note 21.[2] Inflammatory skin conditions listed in Guideline Note 21 include: psoriasis, atopic dermatitis, lichen planus; Darier disease, pityriasis rubra pilaris, discoid lupus and vitiligo.[2] In adults, these conditions are funded when "severe," as defined by a severe score on a validated tool such as the Dermatology Quality of Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI).[2] In addition, at least 10% of body surface involvement and/or hand, foot, face, or mucous membrane involvement must be present.[2] At the December 2022 P & T Committee meeting, PA criteria were removed for preferred products for patients under the age of 21 years. For non-preferred agents, the provider must submit a PA request and provide documentation that the condition for which the therapy is requested is of sufficient severity that it impacts the patient's health. In addition, the patient must fail to achieve benefit with or have contraindications or intolerance to at least 2 preferred topical agents.

Medicaid Fee-For-Service: Topical Agents for Inflammatory Skin Conditions
Preferred Drugs: Pimecrolimus, Tacrolimus, Calcipotriene, Tazarotene, Corticosteroids
Non-Preferred Drugs (Require PA): Crisaborole Ruxolitinib, Tapinarof, Roflumilast, Coal Tar

Oral and Topical Antifungals

OHP does not fund the treatment of candidiasis of the mouth, skin, nails or dermatophytosis of nail, groin, scalp, and other dematophytosis in immune competent adults. Topical antifungal agents are solely indicated for these and other related non-funded conditions. Minor fungal infections of skin, such as dermatophytosis and candidiasis, are only funded when complicated by an immunocompromised host. Prior authorization is required for griseofulvin, itraconazole, and terbinafine due to limited usage beyond onychomycosis, which is non-funded.

At the December 2022 P & T Committee meeting, PA criteria were revised for antifungals in children and adolescents to accommodate an individual review up to their 21st birthday. A case-by-case review for members covered under the EPSDT program will be implemented 1/1/23 for requests to treat non-funded fungal conditions. The provider must submit a PA request and provide documentation that the condition for which the therapy is requested is of sufficient severity that it impacts the patient's health. In addition, the patient must fail to achieve benefit with or have contraindications or intolerance to at least 2 preferred agents.

Medicaid Fee-For-Service: Oral and Topical Antifungals
Preferred Oral Drugs: Clotrimazole, Fluconazole, Nystatin
Nonpreferred Oral Drugs (Require PA): Flucytosine, Griseofulvin Ibrexafungerp, Isavuconazonium, Itraconazole, Ketoconazole, Otsceconazole, Posaconazole, Terbinafine, Voriconazole

Preferred Topical Drugs: Miconazole, Nystatin
Non-Preferred Topical Drugs (Require PA): Butenafine, Ciclopirox, Clotrimazole, Econazole, Ketoconazole, Miconazole, Naftifine, Nystatin, Oxiconazole, Tavaborole, Terbinafine, Tolnafate

Acne

Acne conglobata, acne fulminans, and severe cystic acne are covered conditions under the OHP. Treatment for acne may include a variety of agents such as topical medications (i.e., retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic or topical antibiotics (i.e., doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim, dapsone), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.[3] There is a quantity limit of two, 14-day supplies within a 3-month time period for oral tetracyclines to restrict their use to OHP-funded diagnoses in adults and children. However, providers now have an explicit pathway to approval for acne indications under the EPSDT benefit.

At the December 2022 P & T Committee meeting, PA criteria were revised for acne in children and adolescents to accommodate the individual review for children and adolsescents up to their 21st birthday. A PA is still required for preferred products. A case-by-case review for members covered under the EPSDT program will be implemented 1/1/23 for requests to exceed the tetracycline quanity limit. The provider must submit a PA request and provide documentation that the condition for which the therapy is requested is of sufficient severity that it impacts the patient's health. In addition, the patient must fail to achieve benefit with or have contraindications or intolerance to at least 2 preferred agents.

Medicaid Fee-For-Service Patients: Acne Treatments
Preferred Topical Drugs (Require PA): Adapalene, Azelaic Acid, Benzoyl Peroxide, Clindamycin, Dapsone, Erythromycin, Sulfaceamide, Tretinoin
Non-Preferred Topical Drugs (Require PA): Clascoterone,Tazarotene, Trifarotene

Preferred Oral Drugs: Isotretinoin
Preferred Oral Tetracyclines (Quantity Limit): Doxycycline, Tetracycline
Non-Preferred Oral Tetracyclines (Require PA): Minocycline, Omadacycline

Conclusion

As the ESPDT benefit requirements go into effect on 1/1/2023, children and adolescents will be eligible for coverage of medications deemed medically necessary and medically appropriate on a case-by-case basis up to their 21st birthday. Prior authorization criteria that impact unfunded conditions such as allergic rhinitis, mild-to-moderate inflammatory conditions, mild-to-moderate acne, and dermatophytosis have been updated by the P and T Committee to reflect the ESPDT benefit in appropriate OHP fee-for-service members. As additional medication classes are reviewed, the P and T Committee with continue to modify PA criteria to accommodate individual review under the EPSDT benefit. In the interim, a provider may request an EPSDT review for an individual member for drug classes that have not been updated. Additional EPSDT resources and links to internet resources are listed below. Additional questions can be emailed directly to: **EPSDT.Info@odhsoha.oregon.gov**

Oregon Health Authority EPSDT Program: Early and Periodic Screening, Diagnostic and Treatment Program

Oregon Administrative Rule 410-130-0245: OHA Early and Periodic Screening, Diagnostic and Treatment Program

Medicaid.gov: Early and Periodic Screening, Diagnostic, and Treatment

Peer Reviewed By: Jessica Ickes, MPA; OHA Medicaid Policy Unit, EPSDT/Children's Policy Analyst

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OREGON HEALTH AUTHORITY

DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES

Updated: June 2023

MISSION:

To encourage safe, effective, and innovative drug policies that promote high value medications for patients served by the Oregon Health Plan (OHP) and other health care programs under the Oregon Health Authority (OHA) by evidence-based committee review of drug use research, clinical guidance and education.

DUTIES:

As defined by Oregon Revised Statutes (Chapter 414) the Pharmacy and Therapeutics (P&T) Committee was established to perform functions previously fulfilled by the Drug Use Review Board and Health Resources Commission. Responsibilities of the P&T committee include:

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the OHA for drugs to be included on the preferred drug list (PDL).
    a. The P&T Committee may direct a Subcommittee to prepare these reviews.
2. Advise the OHA on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.
3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.
4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs. Meeting materials including written public comments, recordings, documents, and minutes remain publicly available online after the meeting. Comments are subject to Oregon public records law and should not disclose identifiable, personal health information.
5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.
6. Consider input from Mental Health Clinical Advisory Group (MHCAG) on topics involving mental health. The Mental Health Clinical Advisory Group can make recommendations to both the Oregon Health Authority and the Pharmacy and Therapeutics Committee for:
    a. Implementation of evidence-based algorithms.
    b. Any changes needed to any preferred drug list used by the authority.
    c. Practice guidelines for the treatment of mental health disorders with mental health drugs.
    d. Coordinating the work of the group with an entity that offers a psychiatric advice hotline.
7. Guide and approve meeting agendas.

8. Periodically review and update operating procedures and evidence grading methods as needed.

AD HOC SUBJECT MATTER EXPERT INVOLVEMENT:

1. The Director shall appoint an ad hoc expert to the P&T Committee when:
    a. The P&T Committee determines it lacks current clinical or treatment expertise with respect to a particular therapeutic class; or
    b. An interested outside party requests appointment and demonstrates to the satisfaction of Oregon Health Authority ~~the Director~~ that the P&T Committee lacks necessary clinical knowledge or ~~treatment~~subject matter expertise with respect to a particular therapeutic class. All such requests must be made at least 21 calendar days before the P&T Committee meeting at which the class will be discussed.
    c. Requests for consideration of subject matter expert appointment may be sent by email to OHA.pharmacy@odhsoha.oregon.gov. Requests must identify the clinical topic under review and rational for why an ad hoc subject matter expert would be necessary to add to the P&T Committee.
    d. Ad hoc subject matter experts will have the same requirements, duties, and responsibilities as current P&T Committee members.
    ~~c.~~e. Subject matter experts must be licensed and actively practicing in Oregon.

2. The subject matter~~medical~~ experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of confidential pricing information or other conditions for the inclusion of a drug on the PDL. The subject matter~~medical~~ experts may participate but may not vote in any other activities of the committee during the meeting.

3. P&T Committee staff also may engage relevant health care professionals with clinical specialty to review evidence summary documents prepared for the P&T Committee~~serve as expert reviewers~~, in addition to the ad- hoc subject matter experts, if needed.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.
2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. Elections shall be held the first meeting of the calendar year.
3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.
4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.
5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual prescribers or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug pricing information to inform the recommendations regarding inclusion of drugs on the Practitioner-Managed Prescription Drug Plan (PMPDP) or any preferred drug lists adopted by the OHA.
6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the OHA Director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.

7. Agenda items for which there are no recommended changes based on the clinical evidence may be included in a consent agenda.

    a. Items listed under the consent agenda will be approved by a single motion without separate discussion. If separate discussion is desired, that item will be removed from the consent agenda and placed on the regular business agenda.
    b. Consent agenda items may include (but are not limited to) meeting minutes, drug class literature scans, and abbreviated drug reviews for unfunded conditions.

8. The Oregon Health Authority and P&T Committee are committed to creating a public meeting environment that is inclusive, welcoming, and respectful for all P&T Committee members, staff, and public attendees. Some general guidance and expectations for respectful meeting conduct include:
    a. Attendees of any P&T Committee meeting are expected to behave in a professional, honest, and ethical manner.
    b. Abusive, aggressive, and disrespectful language or behavior is not welcome at meetings. Staff have the authority to mute meeting participants or remove them from the meeting if they engage in this behavior.
    c. If you have a concern regarding your experience during a meeting, please help staff create an inclusive environment by sharing your experience, concerns, and feedback. Feedback can be submitted to osupharm.di@oregonstate.edu.

CONFLICT OF INTEREST POLICY:

The P&T Committee will function in a way that ensures the objectivity and credibility of its recommendations.

1. All potential initial committee members, staff members and consultants, future applicants, expert or peer reviewers, and ad-hoc subject matter ~~medical~~ experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process and annually during their appointment. Any changes in status ~~which~~ must be updated promptly ~~with any changes in status~~.

2. Staff members are required to have no financial conflicts related to any pharmaceutical industry business for duration of work on P&T projects.

3. All disclosed conflicts will be considered before an offer of appointment is made.

4. If any material conflict of interest is not disclosed by a member of the P&T Committee on his or her application or prior to participation in consideration of an affected drug or drug class or other action of the Committee, that person will not be able to participate in voting decisions of the affected drug or drug class and may be subject to dismissal. Circumstances in which conflicts of interest not fully disclosed for peer reviewers, ad-hoc experts, or persons providing public comment will be addressed on a case by case basis.

5. Any person providing public testimony are also requested to disclose all conflicts of interest including, but not limited to, industry funded research prior to any testimony pertaining to issues before the P&T Committee. This includes any relationships or activities which could be perceived to have influenced, or that would give the appearance of potentially influencing testimony.

PUBLIC COMMENT:

1. The P&T Committee meetings will be open to the public.

2. The P&T Committee shall provide appropriate opportunity for public testimony at each meeting.

a. Testimony can be submitted in writing or provided in-person. Persons planning to provide oral testimony during the meeting are requested to sign up and submit a conflict of interest form no later than 24 hours prior to the start of the meeting.

b. Maximum of 3 minutes per speaker/institution per agenda item

   i. Information that is most helpful to the Committee is evidence-based and comparative research, limited to new information not already being reviewed by the Committee.
   ii. Oral presentation of information from FDA-approved labeling (i.e., Prescribing Information or "package insert") is not helpful to the Committee.

c. Please address written testimony related to final posted documents to the P&T Committee. Interested parties may submit written testimony on agenda items being considered by the P&T committee through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management). Written testimony that includes clinical information should be submitted at least 2 weeks prior to the scheduled meeting to allow staff and Committee members time to review the information.

d. Written documents provided during scheduled public testimony time of P&T Committee meetings will be limited to 2 pages of new information that was not included in previous reviews. Prescribing Information is not considered new information; only clinically relevant changes made to Prescribing Information should be submitted.

e. If committee members have additional questions or request input from public members during deliberations after the public comment period, members of the public may be recognized at the discretion of the committee chair to answer questions of the committee or provide additional commentary.

3. Written public comment is welcome from all interested parties on draft documents posted prior to the meeting.
   a. Written public comments submitted during the draft comment period are only considered by staff in order to prepare final documents. Only written public comment submitted based on final documents will be submitted to the P&T Committee for consideration.
   b. Interested parties may submit written testimony on posted draft documents through the public comment link found on the P&T Committee website: (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management).

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the PDL and clinical prior authorization criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices. For detailed description of review standards, preferred sources of evidence, and evidence grading methods, see Quality Assessment Tool and Evidence Grading Methods.

2. Final documents as outlined in Chapter 414 of the Oregon Revised Statutes shall be made publicly available at least 30 days prior to review by the P&T Committee. Posted documents will include the agenda for the

meeting, a list of drug classes to be considered, and background materials and supporting documentation which have been provided to committee members with respect to drugs and drug classes that are before the committee for review.

DRUG AND DRUG CLASS REVIEWS:

1. Drug Class Reviews and New Drug Evaluations:

    a. The P&T Committee will review drugs and drug classes that have not been previously reviewed for PDL inclusion or for clinical PA criteria and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

    b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.
        i. Until new drugs are reviewed by the P&T Committee, drugs meeting the following criteria will be reviewed to ensure they are used appropriately for an FDA-approved or compendia-supported indication, with FDA-approved dosing, and that the indication is funded by the OHP:
            a. A new drug in a drug class with clinical prior authorization criteria.
            b. A new drug used for a non-funded condition on the HERC Prioritized List of Health Services.
            c. A new drug not in a PDL class with existing PA criteria identified by the reviewing pharmacist during the weekly claim processing drug file load costing more than $5,000 per claim or $5,000 per month.

    c. Line Extension and Combination Product Policy
        i. Line extensions include new strengths or new formulations of an existing drug.
            1. When a new strength or formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply until the new strength or formulation is presented to the P&T Committee for review.
            2. If a new strength or formulation becomes available for an existing preferred drug and the new product significantly differs from the existing medication in clinical uses or cost, the drug will not be preferred until the drug is reviewed by the P&T Committee.
        ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, the product will be designated a non-preferred drug until the P&T Committee reviews the combination product.
        iii. When a product becomes available that is a biosimilar for one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee reviews the product. A complete list of biological products and biosimilar products can be accessed at the FDA's Purple Book website.

2. Drug Class Literature Scans and Abbreviated Drug Reviews:

a. Literature of drug classes that have previously been reviewed for the PDL will be scanned and evaluated as needed to assess the need to update drug policies based on clinically relevant information and significant changes in costs published since the last review.
b. Abbreviated drug reviews will evaluate drugs for unfunded conditions. Evidence supporting these reports is derived primarily from information in the product labeling.

Mental Health Clinical Advisory Group

Research Methods

House Bill 2300 (2017) and Senate Bill 138 (2019)

- The MHCAG will develop evidence-based algorithms for mental health treatments
- Algorithms for mental health drugs must consider the following:
    - Efficacy and Safety
    - Cost
    - Patient-specific factors
- Algorithms for mental health drugs must be based on:
    - Peer-reviewed medical literature
    - Observational studies
    - Health economic analyses
    - Input from patients and physicians
    - Any other information that the MHCAG deems appropriate
- The MHCAG makes recommendations to the OHA Pharmacy and Therapeutics Committee on:
    - Implementation of evidence-based treatment algorithms
    - Changes to any preferred drug list used by OHA
    - Practice guidelines for the treatment of mental health disorders with mental health drugs
- All agencies of state government are directed to assist the MHCAG in the performance of their duties
- Mental health drugs in this context include prescription drugs within Standard Therapeutic Classes 07 (ataractics, tranquilizers) and 11 (psychostimulants, antidepressants), lamotrigine and divalproex

The MHCAG Mission

Develop high-quality, clinically relevant behavioral health treatment algorithms based on best available evidence, patient values and current health inequities.

The Research Methods

1. Develop specific clinical research questions
    a. Determines scope, defined and focused
    b. Identify PICOS
        i. Population: populations based on demographic characteristics and clinical diagnoses; include marginalized populations based on race, ethnicity and other factors in which evidence would help address existing health inequities
        ii. Intervention: the specific treatment that needs to be reviewed
        iii. Comparator: fair and reasonable treatment comparison

iv. Outcomes: clinically important outcomes assessed at appropriate timeframe
v. Setting: provider type and level of care

2. Identify high quality systematic reviews from the following preferred sources:
    i. Drug Use Research & Management Program (DURM) at Oregon State University College of Pharmacy
    ii. Drug Effectiveness Research Project (DERP) at the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University
    iii. Agency for Healthcare Research and Quality (AHRQ)
    iv. Canadian Agency for Drugs and Technologies in Health (CADTH)
    v. National Institute for Clinical Excellence (NICE)
    vi. BMJ Clinical Evidence
    vii. U.S. Department of Veterans Affairs/Department of Defense (VA/DoD)
3. Identify other relevant literature from biomedical databases using appropriate search criteria
    a. Databases include: MEDLINE (Ovid, PubMed), Epistemonikos, ACCESSSS, NCBI Bookshelf
4. The MHCAG relies primarily on high quality systematic reviews and randomized controlled trials (RCT) to assess efficacy and harms treatment outcomes.
    a. High-quality systematic reviews meet AMSTAR II criteria (see **Appendix 1**).
    b. The internal validity of RCTs is assessed using a modified Cochrane Risk of Bias tool (see **Appendix 2**).
    c. FDA analyses, if available, may also be considered to complement published studies
    d. Research will be based on hierarchy of evidence:
        i. Systematic reviews (high quality)
        ii. Randomized, controlled trial (high quality)
        iii. Large, longitudinal, controlled cohort studies (especially for safety outcomes)
        iv. Poorer quality systematic reviews and controlled trials
        v. Case-control studies
        vi. Cross-sectional studies
        vii. Unpublished controlled studies (e.g., posters, abstracts, presentations, etc.)
        viii. Non-controlled studies
            1. Surveys
            2. Case series
            3. Case reports
    e. Large observational studies and systematic reviews of observational studies can be used to evaluate long-term safety outcomes
    f. Expert opinion may be considered to answer very specific research questions that cannot be answered by controlled studies
    g. Studies which evaluate clinically meaningful outcomes will be emphasized over studies which evaluate proxies for these outcome (surrogate endpoints)
        i. Mortality
        ii. Morbidity
        iii. Quality of life
        iv. Function
        v. Symptoms

   h. Studies which evaluate U.S. populations, in particular populations from historically marginalized U.S. communities and groups (BIPOC, houseless, Medicaid, etc.) will also be emphasized

5. The MHCAG will utilize high-quality clinical practice guidelines to complement outcomes data found in the primary literature
   a. Systematically developed with high standards using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach
   b. Provides transparent process using evidence and other data to make recommendations
   c. Thoroughly researched and cited using multiple relevant references
   d. Meets the modified AGREE II-GRS criteria (see **Appendix 3**)
6. GRADE the evidence
   a. GRADE (Grading of Recommendations, Assessment, Development and Evaluations)
      i. A transparent, systematic framework for developing and presenting summaries of evidence
      ii. Quality of evidence is applied to each outcome researched, based on the clinical research questions
   b. Grade certainty ratings:

Certainty	Interpretation
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The true effect is probably close to the estimated effect
High	The true effect is similar to the estimated effect

   c. By necessity there is a considerable amount of subjectivity in each GRADE
   d. Assess 5 factors across the individual studies that are sufficiently large enough to affect certainty in an outcome and downgrade an initial certainty GRADE of High (RCT) or an initial certainty GRADE of Low (observational studies) one level lower
      i. Risk of bias: allocation concealment, blinding, attrition
      ii. Imprecision: 95% confidence intervals encompass a reasonable range
      iii. Inconsistency: effect estimate similar across studies
      iv. Indirectness: applicability of patients, intervention, outcomes and setting
      v. Publication bias: missing evidence, study funding
   e. Certainty may be rated up for: large magnitude of effect; obvious dose-response gradient; when all residual confounding would decrease the magnitude of effect (in situations with an effect); or at the majority judgment of MHCAG when significant clinical experience with the treatment and patient preferences are considered.

APPENDIX 1. Methods to Assess Quality of Systematic Reviews.

The AMSTAR II was developed and shown to be a reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable".

High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies was not assessed or considered when conclusions were formulated (#9 and #13)). In general, a high-quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include: DURM; DERP; AHRQ; NICE; VA/DoD; CADTH; and BMJ Clinical Evidence.

Ref. *Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008*. doi: 10.1136/bmj.j4008.

AMSTAR II Quality Scoring Template			
1)	**Did the research questions and inclusion criteria for the review include the components of PICO?** **For Yes**: □ Population □ Intervention □ Comparator group □ Outcome	Optional (recommended) □ Timeframe for follow-up	□ Yes □ No
2)	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** **For Partial Yes:** The authors state that they had a written protocol or guide that included ALL the following: □ review question(s) □ search strategy □ inclusion/exclusion criteria □ risk of bias assessment	**For Yes:** As for partial yes, plus the protocol should be registered and should also have specified: □ meta-analysis/synthesis plan, if appropriate, and □ plan for investigating causes of heterogeneity □ justification for any deviations from the protocol	□ Yes □ Partial Yes □ No
3)	**Did the review authors explain their selection of the study designs for inclusion in the review?** **For Yes**, the review should satisfy ONE of the following: □ Explanation for including only RCTs; OR □ OR Explanation for including only non-randomized studies of interventions (NRSI) □ OR Explanation for including both RCTs and NRSI		□ Yes □ No
4)	**Did the review authors use a comprehensive literature search strategy?** **For Partial Yes** (all the following): □ searched at least 2 databases (relevant to research question) □ provided key word and/or search strategy □ justified publication restrictions (e.g. language)	**For Yes**, should also have (all the following): □ searched the reference lists / bibliographies of included studies □ searched trial/study registries □ included/consulted content experts in the field	□ Yes □ Partial Yes □ No

		□ where relevant, searched for grey literature □ conducted search within 24 months of completion of the review	
5)	**Did the review authors perform study selection in duplicate?** **For Yes,** either ONE of the following: □ at least 2 reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include □ OR 2 reviewers selected a sample of eligible studies and achieved good agreement (at least 80%), with the remainder selected by one reviewer.		□ Yes □ No
6)	**Did the review authors perform data extraction in duplicate?** **For Yes,** either ONE of the following: □ at least 2 reviewers achieved consensus on which data to extract from included studies □ OR 2 reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80%), with the remainder extracted by one reviewer.		□ Yes □ No
7)	**Did the review authors provide a list of excluded studies and justify the exclusions?** **For Partial Yes:** □ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	**For Yes, must also have:** □ Justified the exclusion from the review of each potentially relevant study	□ Yes □ Partial Yes □ No
8)	**Did the review authors describe the included studies in adequate detail?** **For Partial Yes** (ALL the following): □ described populations □ described interventions □ described comparators □ described outcomes □ described research designs	**For Yes,** should also have ALL the following: □ described population in detail □ described intervention in detail (including doses where relevant) □ described comparator in detail (including doses where relevant) □ described study's setting □ timeframe for follow-up	□ Yes □ Partial Yes □ No
9)	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in studies that were included in the review?**		
RCTs	**For Partial Yes,** must have assessed RoB from: □ unconcealed allocation, and □ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	**For Yes,** must also have assessed RoB from: □ allocation sequence that was not truly random, and □ selection of the reported result from among multiple measurements or analyses of a specified outcome	□ Yes □ Partial Yes □ No □ Includes only NRSI
NRSI	**For Partial Yes,** must have assessed RoB: □ from confounding, and □ from selection bias	**For Yes,** must also have assessed RoB: □ methods used to ascertain exposures and outcomes, and □ selection of the reported result from among multiple measurements or analyses of a specified outcome	□ Yes □ Partial Yes □ No □ Includes only RCTs
10)	**Did the review authors report on the sources of funding for the studies included in the review?** **For Yes:** Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies		□ Yes □ No

11)	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**	
RCTs	**For Yes:** ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☐ No meta-analysis conducted
NRSI	**For Yes:** ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	
	For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☐ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**	
	For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☐ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	
	For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☐ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	
	For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☐ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**	
	For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☐ No

APPENDIX 2. Methods to Assess Quality of Randomized Controlled Trials.

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Types of common bias are outlined in Table 1.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	*Systematic differences* between groups in their *baseline characteristics*. Successful ***randomization*** prevents selection bias because **allocation concealment** is implemented. How participants are allocated to groups must be specified, based on some chance (random) process. Furthermore, steps are taken to ensure group assignments are random by preventing knowledge of forthcoming group allocation.
Performance Bias	*Systematic differences* between groups in the *care provided*, or in exposure to factors other than the primary study intervention. **Blinding study participants and healthcare providers** after group allocation reduces the risk that knowledge of which intervention was received affected the outcomes. Effective blinding ensures all groups receive a similar care experience, including ancillary treatments and diagnostic investigations, and minimizes deviations from the study protocol.
Detection Bias	*Systematic differences* between groups in how study **endpoints are assessed**. **Blinding study investigators** reduces the risk that knowledge of which intervention was received, rather than the intervention itself, affected measurement of study endpoints.
Attrition Bias	*Systematic differences* between groups in *study withdrawals*, either by exclusion or attrition. ***Withdrawals*** from the study lead to incomplete outcome data. ***Exclusions*** refer to situations in which participant data are omitted from analyses despite being available to investigators. ***Attrition*** refers to situations in which outcome data are not available (missed appointments or other protocol deviation, or early study discontinuation).
Reporting Bias	The *selective reporting* of *pre-specified* endpoints based on the results found. Reporting bias may arise if results of pre-specified endpoints are omitted or are measured differently or distorted in any way from what was explicitly described in the protocol. Reporting bias may also be introduced when primary endpoints in which statistically significant differences between groups are not found are **selectively reported** while secondary endpoints which found statistically significant differences are over-emphasized.
Other Biases	Other potential sources of bias include investigator's conflicts of interest and study funding sources, which should be collected and presented in the publication. Other biases related to trial designs can be introduced (eg, carry-over from cross-over

	trials, recruitment bias in cluster-randomized trials, or sources of bias from single-centered trials or particular clinical settings).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Each risk of bias domain is assessed and determined to be LOW, HIGH, or UNCLEAR (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix x**).

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table	Sequence generated by: • Date of birth • Admission date • Patient identifier number • Alternating numbers	Method of randomization not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Group allocation cannot be predicted because: • Centrally allocated • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Group allocation may be predicted because: • Open allocation • Drug containers may differ in appearance • Envelopes without appropriate safeguards	Method of concealment not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics Note: Statistical tests of baseline characteristics are not helpful.	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate allocation concealment or failed randomization.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, medical/surg history, concurrent meds)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Standard of care was not consistent across all groups or sites.	• Study participants could not identify study assignment because blinding was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Open-label or incomplete blinding • Observed differences in appearance, taste/smell or adverse effects between groups may have broken blinding • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Blinding process not described or insufficient information to permit definitive judgment
DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Investigators who analyzed data un-blinded	• Blinding of data assessors was ensured and unlikely broken	• No blinding or blinding potentially broken, which likely influenced effect estimates because of	Blinding process not described or insufficient information to permit definitive judgment

	• No data blinding or incomplete blinding, but effect estimate unlikely influenced by clearly defined objective endpoints and large magnitude of difference between groups	inconsistencies between efficacy endpoints or subjective endpoints not well defined.	
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High withdrawal rate (eg, >10% for short-term studies; >20% for longer-term studies) • Difference in attrition >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed for superiority trials • Intention-to-treat and per-protocol analyses performed and compared for non-inferiority trials • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.) • Reasons for missing outcome data unlikely to influence effect estimates	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Selective reporting of endpoints	• Study protocol is available and was followed all pre-specified primary and secondary endpoints are reported • Study protocol is not available, but all endpoints are reported as pre-specified in the study methods	• Not all pre-specified primary and secondary endpoints reported • Primary endpoint(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary endpoint(s) not pre-specified or statistical analyses not described in methods	Insufficient information to make determination

		• Inappropriate over-emphasis of positive secondary endpoints in study with negative primary endpoint	
OTHER BIASES			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of other biases not described in the categories above	• Investigators and authors report no conflicts of interest or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest with investigators or authors based on funding source • Study sponsor is involved in trial design, data analysis, and publication of data • Interventions in run-in period may impact effect of interventions post-randomization • Recruitment bias in cluster-randomized trials • Early study termination based on positive results • Carry-over effects in cross-over trials • Protocol deviation based on interim results	• Conflicts of interest declarations or funding sources not reported • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (directness) of the evidence to Oregon's populations (**Table 3**).

Table 3. PICOS Domains that Determine Applicability

PICOS Domain	Conditions that Limit Applicability
Patients	• Narrow eligibility criteria and broad exclusion criteria • Significant differences between the demographic characteristics of the study population and the Oregon's populations of interest • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in Oregon's populations of interest
Interventions	• Dose, frequency of administration, formulation not reflective of clinical practice • Intensity/delivery of interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparators	• Inadequate dose or frequency of administration of comparator • Use of inferior or substandard comparator relative to other alternatives
Outcomes	• Short-term or surrogate endpoints assessed • Instrument used to assess endpoints is difficult to use or impractical to implement in clinical practice • Composite endpoint used that mix outcomes of different significance
Settings	• Standards of care in study setting differ markedly from clinical practice

	• Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care provided from specialists does not reflect clinical practice where intervention is likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (updated March 2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

APPENDIX 3. Methods to Assess Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The consolidated AGREE II Global Rating Scale (GRS) is an easy-to-administer, validated instrument that consists of 4 items (**Table 4**). Each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. In general, a high-quality clinical practice guideline will score 5-7 points on each component of the AGREE II-GRS.

Table 4. AGREE II Global Rating Scale (modified)**.**

	ITEM	DESCRIPTION
PROCESS DEVELOPMENT		
1	Rate the guideline development methods. **SCORE:**	• Appropriate stakeholders were involved in the development of the guideline. • The evidence-base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.
PRESENTATION STYLE		
2	Rate the guideline presentation. **SCORE:**	• The guideline was well organized. • The recommendations were easy to find.
CLINICAL VALIDITY		
3	Rate the guideline recommendations. **SCORE:**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
COMPLETENESS OF REPORTING		
4	Rate the completeness of reporting, editorial independence. **SCORE:**	• The information is complete to inform decision-making. • The guideline development process is transparent and reproducible.
5	The views of the funding body did not influence the content of the guideline. **SCORE:**	• The name of the funding body or source of funding is explicitly stated (or explicit statement of no funding) • There is a statement that the funding bodies did not influence the content of the guideline, or at least *how* the guideline development group addressed *potential* influence from the funding bodies.
6	Competing interests of guideline development group members were recorded and addressed. **SCORE:**	• A description of the types of competing interests is considered. • Methods by which potential competing interests were sought. • Competing interests are described. • How the competing interests influenced the guideline process and development of recommendations is described.

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Review Standards and Methods for Quality Assessment of Evidence

Updated: February 2023

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug and drug class reviews based on sound evidence-based research and processes widely accepted by the medical profession. These evidence summaries inform the recommendations for management of the preferred drug list (PDL) and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

2. The types of reviews may include, but are not limited to, the following:

Type of Review	Rationale for Review
Abbreviated Drug Review	New drug with evidence only for non-funded condition(s)
Class Literature Scan	Used when limited literature is found which would affect clinical changes in PDL status or PA criteria based on efficacy or safety data (may include new drug formulations or expanded indications if available literature would not change PDL status or PA criteria). Provides a summary of new or available literature, and outcomes are not evaluated via the GRADE methodology listed in **Appendix D**.
New Drug Evaluation (NDE)	Single new drug identified and the PDL class was recently reviewed, or the drug is not assigned to a PDL drug class
Class Review	New PDL class
Class Update	New systematic review(s) and clinical trials identified that may inform change in PDL status or clinical PA criteria in an established PDL class
Class Update with New Drug Evaluation	New drugs(s) or indication(s) also identified (excludes new formulations, expanded indications, biosimilars, or drugs for unfunded indications)
DERP Summary Report	New DERP report which evaluates comparative evidence
Drug Use Evaluation	Analysis of utilization trends in FFS population in order to identify safety issues or inform future policy decisions
Policy Evaluation	Evaluation safety, efficacy, and utilization trends after implementation of a policy to identify areas for improvement
Prior Authorization Update	To evaluate targeted updates to PA criteria based on current policy guidance from the Health Evidence Review Commission, recommendations from the Mental Health Clinical Advisory Group, or expanded labeling from the FDA

3. The P&T Committee will rely primarily on high quality systematic reviews and randomized controlled trials in making its evidence summary recommendations. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence.

4. Emphasis will be placed on the highest quality evidence available. Poor quality trials, systematic reviews or guidelines are excluded if higher quality literature is available and results offer no additional value. Unless the trial evaluates an outcome or comparison of high clinical importance, individual RCTs with the following study types will be excluded from class updates, class reviews, and literature scans:
    a. Non-comparative, placebo-controlled trials
    b. Non-inferiority trials
    c. Extension studies
    d. Poor quality studies (as assessed in **Appendix A**)

5. Individual drug evaluations rely primarily on high quality RCTs or clinical trials used for FDA approval. Evidence from poor quality RCTs may be included if there is no higher quality evidence available.

6. Phase 2 trials may be considered if there is a compelling reason to include, such as use for FDA approval. Preference will be given for inclusion of applicable phase 3 and 4 trials over earlier phase studies. If fully published, of adequate duration, and with appropriate clinical outcome measures, authors may include phase 2 studies if phase 3 or 4 trials are inadequate or when direct comparative evidence and/or dose response are reported in a comparable population to available phase 3 or 4 studies.

7. The following are preferred sources that provide high quality evidence at this time:

    a. Drug Effectiveness Review Project at Oregon Health & Science University (OHSU)
    b. U.S. Department of Veterans Affairs/Department of Defense
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. National Institute for Clinical Excellence (NICE)
    f. Scottish Intercollegiate Guidelines Network (SIGN)
    ~~f.~~g. Oregon Mental Health Clinical Advisory Group (MHCAG)

8. The following types of evidence are preferred and will be considered only if they are of high methodological quality as evaluated by the quality assessment criteria below:

    a. Systematic reviews of randomized controlled trials
    b. Direct comparative randomized controlled trials (RCTs) evaluating clinically relevant outcomes; placebo-controlled studies not related to initial FDA-drug approval or new indications may be considered if likely to impact current policy
    c. FDA review documents
    d. Clinical Practice Guidelines developed using explicit evidence evaluation processes

9. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

    a. Observational studies, case reports, case series
        i. However, observational studies and systematic reviews of observational studies will be included to evaluate significant safety data beyond the FDA labeling information. Observational studies will only be included when there is not adequate data from higher quality literature.
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents
    c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality compared to other relevant literature, or duplicate information in other materials under review.
    d. Studies not designed to investigate clinically relevant outcomes
    e. Systematic reviews identified with the following characteristics:
        i. Evidence is of poor or very poor quality
        ii. Evidence is of limited applicability to a US population
        iii. Systematic review does not meet defined applicability criteria (PICOTS criteria) for the topic
        iv. Systematic review is of poor methodological quality as evaluated by AMSTAR II criteria (see **Appendix B**)
        v. Evidence is based on indirect comparisons from network meta-analyses
        vi. Conflicts of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)
    f. Guidelines identified with the following characteristics:
        i. There is no systematic guideline development method described
        ii. Strength of evidence for guideline recommendations are not provided
        iii. Recommendations are largely based on expert opinion
        iv. Poor methodological quality as assessed in **Appendix C** (AGREE II score is less than 113 points OR modified AGREE II-GRS score is less than 30 points)
        v. Conflict of interest which are considered to be a "fatal flaw" (see quality assessment for conflicts of interest)

QUALITY ASSESSMENT

1. The standard methods used by the DURM faculty to assess quality of evidence incorporated into the evidence summaries for the OHP Pharmacy and Therapeutics Committee are described in detail in **Appendix A-C**.

2. The Cochrane Risk of Bias tool (modified) described in **Appendix A** is used to assess risk of bias (i.e., internal validity) of randomized controlled trials. The quality of non-inferiority trials will be also assessed using the additional criteria for non-inferiority trials in **Appendix A**. Internal validity of clinical trials are graded as poor, fair, or good quality.

3. The AMSTAR II measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Systematic reviews, meta-analyses or guidance identified from 'best sources' listed in **Appendix B** undergo methodological rigor and are considered to be high quality and are not scored for quality using the AMSTAR II tool.

4. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**. If there are concerns regarding applicability of guidelines to the Medicaid population, the AGREE-REX tool is available for use (https://www.agreetrust.org/resource-centre/agree-rex-recommendation-excellence/).

5. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability, or directness, of randomized controlled trials to the OHP population. Detailed guidance is provided in **Appendix A**. Only randomized controlled trials with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries.

6. Emphasis of the review will be on clinically relevant outcomes. The following clinically relevant outcomes are graded for quality: mortality, morbidity outcomes, symptom relief, quality of life, functioning (physical, mental, or emotional), early discontinuation due to adverse events, and severe adverse effects. Surrogate outcomes are considered if directly linked to mortality or a morbidity outcome. Clinically meaningful changes in these outcomes are emphasized.

7. The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm using the GRADE methodology listed in **Appendix D**. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient**. Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

    a. Evidence grades are defined as follows:
        i. High quality evidence: High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
        ii. Moderate quality evidence: Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
        iii. Low quality evidence: Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
        iv. Insufficient evidence: Evidence is not available or too limited to permit any level of confidence in the estimated effect.

8. Conflict of Interest
    a. Conflict of interest is a critical component of quality assessment. A conflict of interest is "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a second interest." Conflict of interest includes any relationships or activities that could be perceived to have influenced or give the appearance of potentially influencing the literature.
        i. Reference: IOM (Institute of Medicine). 2009. *Conflict of Interest in Medical Research, Education, and Practice.* Washington, DC: The National Academies Press.

    b. Conflict of interest analysis for DURM reviews:
        1. Sources will be excluded due to conflict of interest concerns if they contain one of the "fatal flaws" in **Table 1** below.
        2. If no "fatal flaws" exist, an analysis of the conflicts of interest will be completed and any limitations (examples in **Table 1** below) will be first and foremost discussed in the evidence review.
        3. Conflict of interest is also assessed through the Cochrane risk of bias, AMSTAR II, and AGREE tools (**Appendix A, B, and C**).

Table 1. DURM Conflict of Interest Analysis

Type of literature	"Fatal flaws"	If no "fatal flaws" exist, potential limitations to discuss when including the piece of literature	Other considerations- specific to the type of literature
Randomized controlled trial	• Conflict of interest not documented	• Authors or committee members have significant conflicts of interest • Concerning high dollar amounts of conflicts of interest are documented • Mitigation strategies (described in the article or journal/organization policies) are documented but could be more robust	• Higher risk of bias when the study sponsor is the pharmaceutical manufacturer and is included in data analysis and manuscript writing
Systematic review	• Conflict of interest not documented • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* persons with potential conflicts of interest are excluded from the assessment or review process, independent second review of articles considered for inclusion in SR that are reviewed first by their own author who is on the SR team		• May consider funding sources or conflicts of interest for both the systematic review and the included studies
Guideline	• Conflict of interest not documented • Chair has a conflict of interest • Conflict of interest mitigation strategies not documented or are insufficient to mitigate potential bias • *Example mitigation strategies:* excluding persons with significant conflict of interest from the review process, recusing members with significant conflict of interest from voting on recommendations or having them leave the room during the discussion		• Guidelines with "fatal flaws" which are commonly used in practice may be included for clinical context but will not be considered when creating conclusions or recommendations

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Reporting bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).
Other Bias	Other sources of bias may be present depending on conflict of interests and funding sources, trial design, or other specific circumstances not covered in the categories above. Of particular concern is how conflicts of interest and funding sources may potentially bias results. Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. Information about vested interests should be collected and presented when relevant, with specific regard for methodology that might be been influenced by vested interests and which may lead directly to a risk of bias. Additional sources of bias may result from trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the experimental and control interventions get 'mixed', for example if participants pool their drugs).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials; therefore, it is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Conflicts of interest should also be assessed when determining risk of bias. This may be considered part of risk of reporting bias. Funding sources for the trial, conflicts of interest of the authors, and role the study sponsor played in the trial should be considered in this domain.

The quality of each trial will be graded as **good, fair,** or **poor** based on the following thresholds for converting the Cochrane Risk of Bias Tool to AHRQ Standards. A good quality trial will have low risk of bias for all domains. A fair quality trial will have one domain with high risk of bias or 2 domains with unclear bias, with the assessment that the one or more biases are unlikely to influence the outcome, and there are no known limitations which could invalidate results. A poor quality trial will have high risk of bias for one or more domains or have 2 criteria with unknown bias for which there may be important limitations which could invalidate the results or likely bias the outcome. Trials of poor quality will be excluded from review if higher quality sources of evidence are available.

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Systematic differences in how care was provided between groups due to un-blinding of participants or investigators/care providers or because of standard of care was not consistent across all sites.	• Study participants could not identify study assignment because blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • Protocol standardized across all sites and followed consistently	• Study participants could possibly identify study assignment because there was no blinding or incomplete blinding • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups) • Some sites had a different standard of care or varied from protocol which likely influenced effect estimate	Not described or insufficient information to permit definitive judgment

DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	• Outcome data assessors could possibly identify study assignment because no blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, large differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment
ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest • Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	Insufficient information to make determination
OTHER BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**

Evidence of other biases not described in the categories above	• No conflicts of interest present or study sponsor was not involved in trial design, data analysis or publication • No other potential sources of bias identified	• Conflicts of interest are present based on funding source or conflicting interests of authors • Study sponsor is involved in trial design, data analysis, and publication of data • There is a run-in period with pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention • Recruitment bias in cluster-randomized trials with differential participant recruitment in clusters for different interventions • Cross-over trials in which the crossover design is not suitable, there is significant carry-over effects, or incompletely reported data (data reported only for first period) • Conduct of the study is affected by interim results ((e.g. recruiting additional participants from a subgroup showing more benefit) • Deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).	• Conflicts of interest for authors or funding sources are not reported or not described • Insufficient information regarding other trial methodology and design to make a determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Non-inferiority (NI) trials are designed to prove a new treatment is not worse than the control treatment by a pre-determined difference, with a given degree of confidence. The pre-determined margin of difference in non-inferiority trials is defined as delta. Correctly determining this margin is a challenge in the design and interpretation of NI trials. The greatest challenge in use of NI trials is recognizing inappropriate use.

Non-inferiority trials will only be included in evidence summaries when there is a compelling reason to include them, and higher quality evidence is not available. The compelling reason for inclusion will be clearly stated as an introduction to the reporting of the NI trial.

The following template was developed using CONSORT and FDA guidance[1,2] and will be used as a guideline to evaluate non-inferiority studies included in DURM evidence summaries. Unless the trial evaluates an outcome or comparison of high clinical importance, individual non-inferiority trials will be excluded from class updates, class reviews, and literature scans. Evidence from poor quality RCTs may be included in individual drug evaluations if there is no higher quality evidence available. Items in bold (#1-5) are essential to conducting a non-inferiority trial with good methodological rigor. In general, a non-inferiority trial with high quality methods will score a "yes" on most of the components listed below.

Table 4. Non-inferiority Trial Quality Scoring Template

Developed using CONSORT and FDA guidance[1,2] **Use Template to evaluate trials supporting New Drug Evaluations and Class Update Reports** **A high-quality trial will meet all bolded assessments below**	
1. Rationale for choosing comparator with historical study results confirming efficacy (or safety) of this comparator is provided.	□ **Yes** □ **No** □ **Can't answer**
2. Active control (or comparator) represents current standard of care.	□ **Yes** □ **No** □ **Can't answer**
3. Non-inferiority margin was specified a priori and based on statistical reasoning and clinical considerations regarding benefit, risk, and cost.	□ **Yes** □ **No** □ **Can't answer**
4. Noninferiority margin is not larger than the expected difference between active control (or comparator) and placebo.	□ **Yes** □ **No** □ **Can't answer**
5. If a superiority conclusion is drawn for outcome(s) for which noninferiority was hypothesized, the justification for switching is provided and superiority analysis was defined a priori.	□ **Yes** □ **No** □ **Can't answer**
6. Investigator reported both ITT and per-protocol analysis in detail and the results of both analyses demonstrate noninferiority. (If only one analysis is provided, per protocol is subject to less bias than ITT analysis in noninferiority trials.)	□ **Yes** □ **No** □ **Can't answer**
7. Rationale for using a noninferiority design is included (or why it would likely be unethical to conduct a placebo-controlled superiority trial of the new therapy).	□ Yes □ No □ Can't answer
8. Study hypothesis is stated in terms of noninferiority.	□ Yes □ No □ Can't answer
9.Eligibility criteria for participants and the settings in which the data were collected are similar to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
10. Trial is designed to be consistent with historical placebo-controlled trials.	□ Yes □ No □ Can't answer
11. The reference treatment in the noninferiority trial is identical (or very similar) to that in any trial(s) that established efficacy (or safety).	□ Yes □ No □ Can't answer
12. The outcomes in the noninferiority trial are identical (or very similar) to those in any trial(s) that established efficacy (or safety) of the reference treatment.	□ Yes □ No □ Can't answer
13. The lower bound of that CI is clinically significant.	□ Yes □ No □ Can't answer
14. For the outcome(s) for which noninferiority was hypothesized, a figure showing confidence intervals and the noninferiority margin is included.	□ Yes □ No □ Can't answer
15. Results are interpreted in relation to the noninferiority hypothesis.	□ Yes □ No □ Can't answer

References:
1. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *Jama*. 2012;308(24):2594-2604.
2. FDA Industry Guidance for Noninferiority Trials. November 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR II) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 16 components addressed in the measurement tool below, and questions can be scored in one of four ways: "Yes", "Partial Yes", "No", or "Not Applicable". The AMSTAR II is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#4); characteristics of studies not provided (#8); quality of studies were not assessed or considered when conclusions were formulated (#9 and #13)). Other areas identified as important domains in the AMSTAR II criteria include registration of a protocol (#2); justification for excluding individual studies (#7); appropriateness of meta-analysis methods (#11); and assessment of publication bias (#15). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR II tool.

Ref. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); National Institute for Health and Care Excellence (NICE); U.S. Department of Veterans Affairs (VA); and Canadian Agency for Drugs and Technologies in Health (CADTH); and BMJ Clinical Evidence.

AMSTAR II Quality Scoring Template

1) Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- □ Population
- □ Intervention
- □ Comparator group
- □ Outcome

Optional (recommended)

- □ Timeframe for follow-up

□ Yes
□ No

2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:

- □ review question(s)
- □ a search strategy
- □ inclusion/exclusion criteria
- □ a risk of bias assessment

For Yes: As for partial yes, plus the protocol should be registered and should also have specified:

- □ a meta-analysis/synthesis plan, if appropriate, and
- □ a plan for investigating causes of heterogeneity
- □ justification for any deviations from the protocol

□ Yes
□ Partial Yes
□ No

3) Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- □ Explanation for including only RCTs
- □ OR Explanation for including only NRSI
- □ OR Explanation for including both RCTs and NRSI

□ Yes
□ No

4) Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- searched at least 2 databases (relevant to research question)
- provided key word and/or search strategy
- justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- searched the reference lists / bibliographies of included studies
- searched trial/study registries
- included/consulted content experts in the field
- where relevant, searched for grey literature
- conducted search within 24 months of completion of the review

- Yes
- Partial Yes
- No

5) Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- Yes
- No

6) Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- at least two reviewers achieved consensus on which data to extract from included studies
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- Yes
- No

7) Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- Justified the exclusion from the review of each potentially relevant study

- Yes
- Partial Yes
- No

8) Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- described populations
- described interventions
- described comparators
- described outcomes
- described research designs

For Yes, should also have ALL the following:
- described population in detail
- described intervention in detail (including doses where relevant)
- described comparator in detail (including doses where relevant)
- described study's setting
- timeframe for follow-up

- Yes
- Partial Yes
- No

9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from:
- unconcealed allocation, and
- lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- allocation sequence that was not truly random, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- from confounding, and
- from selection bias

For Yes, must also have assessed RoB:
- methods used to ascertain exposures and outcomes, and
- selection of the reported result from among multiple measurements or analyses of a specified outcome

- Yes
- Partial Yes
- No
- Includes only RCTs

10) Did the review authors report on the sources of funding for the studies included in the review?

For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- Yes
- No

11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:
- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- AND investigated the causes of any heterogeneity

- Yes
- No
- No meta-analysis conducted

NRSI	**For Yes:** □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	□ Yes □ No □ No meta-analysis conducted
12)	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** **For Yes:** □ included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	□ Yes □ No □ No meta-analysis conducted
13)	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?** **For Yes:** □ included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	□ Yes □ No
14)	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** **For Yes:** □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	□ Yes □ No
15)	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** **For Yes:** □ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	□ Yes □ No □ No meta-analysis conducted
16)	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** **For Yes:** □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest	□ Yes □ No

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument (www.agreetrust.org) assesses the methodologic rigor in which a guideline is developed and used. The AGREE II is an updated instrument that has been validated. It consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated global rating scale (GRS) was developed, and is generally a reasonable alternative to AGREE II if resources are limited. The AGREE II-GRS instrument consists of only 4 items (**Table 2**). As the AGREE II-GRS does not take into account conflicts of interest, questions 22 and 23 regarding "Editorial Independence" will also be evaluated in conjunction with the AGREE II-GRS. With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II and each component of the AGREE II-GRS.

Table 1. AGREE II Instrument.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**

9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**
11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. AGREE II Global Rating Scale (modified).

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.
5	The views of the funding body have not influenced the content of the guideline. **[SCORE:]**	• Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
6	Competing interests of guideline development group members have been recorded and addressed. **[SCORE:]**	• There should be an explicit statement that all group members have declared whether they have any competing interests. • All competing interests should be listed • There should be no significant competing interests

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:
- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

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Prior Authorization Criteria Update: Low-Dose Quetiapine

Conclusions:

- Quetiapine is not well tolerated in people with generalized anxiety disorder (GAD), but there is moderate quality evidence that extended-release (ER) quetiapine improves anxiety symptoms, improves function and induces remission of GAD, as evidenced by statistically significant improvement in Hamilton Anxiety Scale (HAM-A) scores from multiple randomized placebo-controlled trials.

Policy Recommendations:

- Update clinical prior authorization (PA) criteria to allow coverage of quetiapine ER for GAD, as proposed.

Background and Recommendations from the Mental Health Clinical Advisory Group:

The Mental Health Clinical Advisory Group (MHCAG), tasked by the Oregon legislature to develop evidence-based treatment guidelines for mental health disorders, published a treatment algorithm for GAD in 2023 (see **Appendix 1**). The MHCAG recommend extended-release (ER) quetiapine, in consultation with a mental health provider, as an adjunctive treatment option after other recommended adjuncts have been tried. Current Oregon Health Plan (OHP) fee-for-service clinical PA criteria do not permit coverage of quetiapine ER for GAD. The tolerability and safety of quetiapine is already established: sedation, dyslipidemia, hyperglycemia, weight gain, and rare but fatal arrhythmias from QT prolongation, require routine monitoring and limit broad use of the drug except when needed. This brief review summarizes the efficacy of quetiapine ER in people with GAD to determine if the current clinical PA criteria should be changed to allow off-label coverage of quetiapine ER for GAD when prescribed by, or in consultation with, a mental health provider.

Evidence Summary:

Four high-quality systematic reviews were identified that evaluated the efficacy and tolerability of quetiapine ER for treatment of GAD. Trials compared quetiapine to placebo and SSRIs. The primary efficacy endpoint used to assess improvement in anxiety symptoms, treatment response, and remission was the HAM-A. Study durations were 10 to 14 weeks.

A systematic review and meta-analysis of double-blind, randomized controlled trials (RCTs) reviewed the comparative remission rates and tolerability of medications for GAD. GAD remission rates (HAM-A scores ≤7) and tolerability with quetiapine ER were studied in 4 eligible trials at daily doses of 50 mg, 150 mg and 300 mg.[1] Quetiapine was found to be superior to placebo at inducing remission in patients with GAD (OR 1.88; 95% CI, 1.39-2.55) but was also much less tolerable than placebo, leading to more treatment discontinuations due to adverse events (OR 4.05; 95% CI, 2.89-5.65).[1]

A systematic review and meta-analysis of 3 RCTs (n=2,678) reviewed the efficacy (HAM-A) and tolerability (discontinuation rates due to adverse events) of quetiapine ER in patients with GAD.[2] Mean differences in HAM-A scores were 2.19 points lower (95% CI, -2.94 to -1.45) with quetiapine than with placebo.[2] Quetiapine also resulted in both higher response rates (≥50% HAMA-A reduction) than placebo (RR 1.24; 95% CI, 1.16 to 1.32) and higher remission rates (HAMA-A ≤7) than placebo (RR 1.27; 95% CI, 1.13 to 1.42).[2] The 50 mg, 150 mg, 300 mg daily doses of quetiapine studied all showed statistically significant

reductions in HAM-A scores versus placebo, but only the 50 mg and 150 mg daily doses resulted in statistically significant higher response and remission rates.[2] The 2 eligible trials that compared quetiapine ER to an SSRI did not find statistically significant differences in any efficacy endpoints between the groups studied.[2] Quetiapine was less tolerable than placebo, as evidenced by overall higher discontinuation rates due to adverse events (RR 3.18; 95% CI, 2.52 to 4.00).[2] Only the quetiapine 50 mg daily dose was comparable in tolerability to SSRIs; higher doses were subject to higher discontinuation rates due to adverse events.[2]

A systematic review and meta-analysis analyzed evidence for off-label uses of second-generation antipsychotics in adults, including quetiapine for GAD.[3] The review included some trials that overlapped with the systematic reviews previously described. Data from the trials that could be pooled showed that quetiapine ER resulted in a 26% increase in the chance of treatment response at 8 weeks (≥50% HAMA-A reduction; number needed-to-treat = 8) for quetiapine ER in patients with GAD at daily doses of 50 mg to 300 mg.[3] No differences in efficacy were identified when quetiapine was compared to escitalopram or paroxetine for treatment of GAD.[3]

The most recently published systematic review included clinical trials of all medications that have been studied for treatment GAD, including SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), pregabalin, bupropion, imipramine, mirtazapine, buspirone, hydroxyzine, quetiapine, benzodiazepines and others.[4] By meta-analysis, the study found that quetiapine had the largest effect on HAM-A versus placebo than any of the other medications studied (mean difference vs. placebo: -3.60; 95% CI, -4.83 to -2.39), but it was also poorly tolerated versus placebo as evidenced by higher study discontinuation (OR 1.44; 95% CI, 1.16 to 1.80).[4]

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Medication Treatment for Adults with Generalized Anxiety Disorder

- Generalized Anxiety Disorder (GAD) frequently has a waxing and waning course, so medication treatment should continue for 6-12 months after remission to reduce risk of relapse.[1]
- It is useful to monitor for clinically meaning improvement of symptoms and function using the Hamilton Anxiety Scale (HAM-A), the Generalized Anxiety Disorder-7 (GAD-7), or another validated grading scale routinely used in the provider's practice.
- At any point before or during treatment, immediate referral is needed for patients with severe anxiety and marked functional impairment in conjunction with:
  - Risk of self-harm or suicide, or
  - Significant comorbidity, such as substance misuse, personality disorder or complex physical health problems, or
  - Self-neglect.[2]

This guidance may be helpful to the primary care provider to complement their clinical judgement.

Primary Therapy

First-line Treatment

- The selective serotonin reuptake inhibitors (SSRI) **escitalopram** or **sertraline**, or alternatively the serotonin norepinephrine reuptake inhibitors (SNRI) **duloxetine** or **extended-release venlafaxine**, are recommended as first-line primary treatment for GAD regardless of baseline symptom severity based on high-quality evidence for efficacy (symptoms, remission), fewer drug interactions relative to other SSRIs and SNRIs, and overall tolerability.[1,3-6]
- SSRIs are generally better tolerated at higher doses than SNRIs. Consider the overall side-effect profile, drug interactions, and patient preference before prescribing treatment.

Other Primary Treatment Options

Generally, non-SSRI/SNRI antidepressants lack evidence of effectiveness or may not be well tolerated.[13] However, a few may be worth trying, especially if there are other indications for doing so:

- The tricyclic antidepressant **imipramine** is effective for treatment of GAD.[1,4] However, side effects and potential for toxicity limits its use.
- Limited evidence suggests **extended-release bupropion** may be as effective as escitalopram.[7]

See Appendix for example treatment algorithm.

Adjunctive Therapy

Adjunctive treatment may be effective in adults with GAD who have had an inadequate response (e.g., < 50% improvement in HAM-A) to multiple trials of antidepressants after adequate adherence, dosage and therapy duration (4-6 weeks) are confirmed.[1] However, adjunctive therapy may add additional complexity:

- If improvement occurs with adjunctive therapy, it may be unclear whether it is due to the second medication or the combination of medications.
- Combination therapy also increases risk of adverse effects and drug interactions.

First-line Adjunct Treatment

- The anticonvulsant **pregabalin** is effective for treatment of GAD based on high-quality evidence.[1,3,4,8] Pregabalin is recommended as a first-line adjunct with an SSRI or SNRI, but it can also be used as a primary treatment option for patients who cannot tolerate antidepressants.[2] However, not everyone will tolerate pregabalin well. It is also a controlled substance with potential for abuse.

Second-line Adjunct Treatment

- **Buspirone** may be effective for the treatment of GAD.[1,5] However, there is low quality evidence for effectiveness versus first-line antidepressants, and buspirone has a slow onset of therapeutic effect (4-6 weeks) and short half-life which requires frequent daily dosing.[1]

See Appendix for example treatment algorithm.

Other Adjunct Treatments

- **Extended-release quetiapine**, a second-generation antipsychotic, has moderate evidence for the management of GAD and may be as effective as antidepressants.[10-13] However, sedation, metabolic side effects and poor tolerability limits use.[4,12,13] Quetiapine ER should be reserved after other adjuncts have been tried, and a specialist should be consulted.
- **Hydroxyzine** may be as effective for the treatment of GAD, but sedation, anticholinergic effects, and limited clinical experience are barriers to long-term use.[1,17]
- Benzodiazepines like **diazepam** or **lorazepam** can provide immediate, short-term relief of somatic symptoms of GAD, but at increased risk for adverse events.[3,14,15] This strategy can be especially useful in patients with severe symptoms of GAD during the first weeks of antidepressant treatment.[1]
    - Use with caution for longer than 2 weeks because regular use increases risk of abuse, misuse, addiction, physical dependence and withdrawal reactions.[16]
    - Withdrawal from benzodiazepines after regular use is a complex process and highly variable between individuals. Providers should consult MHCAG guidance for tapering off benzodiazepines.

Medication Dosing for GAD in Older adults and Pregnancy

- Use these medications with great caution in older adults, who are more susceptible to adverse effects of psychoactive medications. Start at low doses and titrate slowly with dose adjustments no more than every 2 weeks. Drug-drug interactions are also more common in older adults who may be on multiple medications which can interact with each other and increase risk for intolerances and adverse effects.

- Many of these medications cross the placenta but there is little documented evidence of teratogenic effects. Until more information is available, administer these medications during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
- A pregnancy registry (National Pregnancy Registry for Antidepressants) is available for antidepressants; healthcare providers can register patients by contacting 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants.
- A North American Antiepileptic Drug (NAAED) Pregnancy Registry has been established to monitor the effects of *in utero* exposure to pregabalin, and patients are encouraged to enroll themselves by calling 1-888-233-2334. Patients may also obtain information on the NAAED website: www.aedpregnancyregistry.org/
- Use benzodiazepines during pregnancy only during serious or life-threatening emergencies where safer drugs cannot be used or are ineffective.

Discontinuation of Treatment

- *Continue treatment of GAD for at least 6-12 months. Do not discontinue more than one medication for GAD at a time, and only after almost all symptoms are gone. Tapering off SSRIs, SNRIs, quetiapine can take 3 to 6 months or longer.* Tapering off benzodiazepines *can take much longer and must be individualized.*

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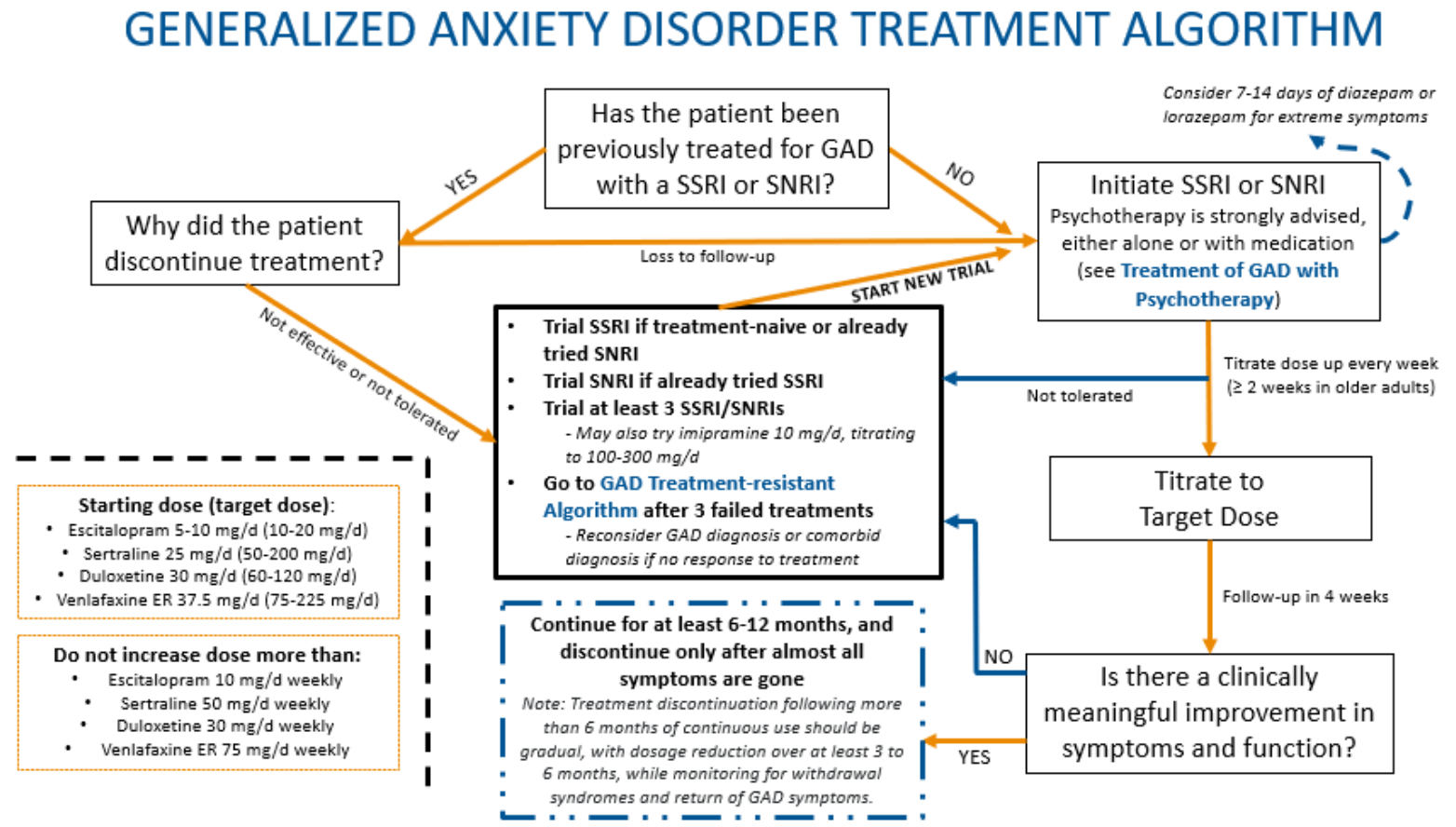
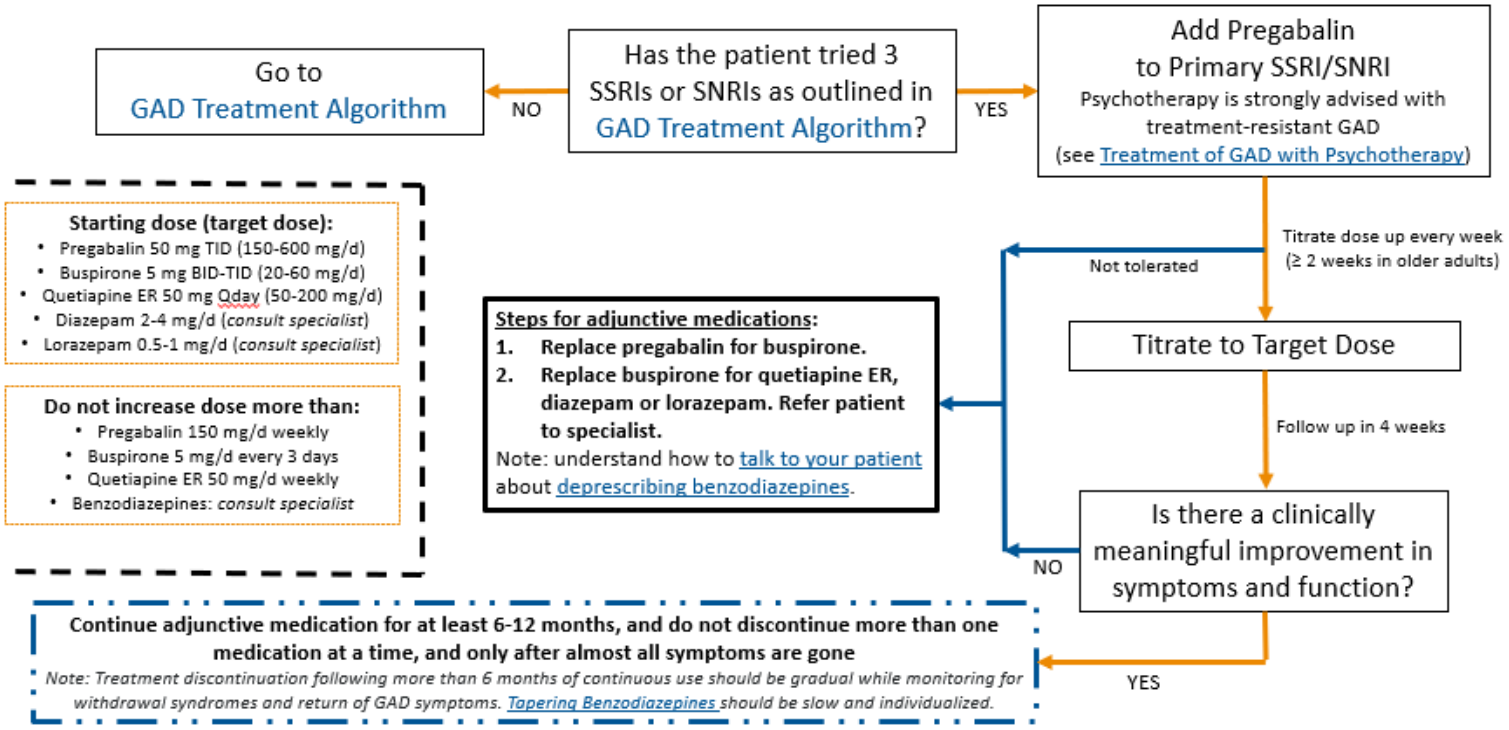
Appendix



GENERALIZED ANXIETY DISORDER TREATMENT-RESISTANT ALGORITHM



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Drug Use Evaluation: Low Dose Quetiapine

Plain Language Summary:

- Quetiapine is a medicine prescribed for many different mental health conditions.
  - Quetiapine can help improve mood and quality of life in people with bipolar disorder or schizophrenia.
  - Quetiapine tablets that provide medicine coverage for an entire day (called extended-release tablets) may also improve anxiety or depression.
  - Some providers also prescribe low doses of quetiapine to improve sleep.
- Quetiapine can have serious long-term side effects, and the risks of treatment may not be worth it in most people.
- The Oregon Health Plan (OHP) currently requires prescribers to provide information to the Oregon Health Authority (OHA) on why a low dose of quetiapine is needed. This process is called prior authorization.
- OHP commonly approves pharmacy claims for low dose quetiapine without delay for:
  - people who have been prescribed other antipsychotic medicines
  - people who have a diagnosis of schizophrenia or bipolar disorder
  - people with prescriptions from a mental health provider
- Under the current policy, there are delays in pharmacy claims approval for:
  - people with depression or anxiety
  - people who have been prescribed antidepressant medicines
- We recommend automatically approving extended-release quetiapine for people who are also prescribed an antidepressant for depression or anxiety.

Research Questions:

- What proportion of patients with claims for low dose quetiapine (<50 mg daily) have compendia-supported diagnoses?
- What proportion of patients with claims for low dose quetiapine are also prescribed other mental health medications?
- What proportion of patients are prescribed low dose quetiapine from a mental health specialist?

Conclusions:

Diagnoses in medical claims

- About 69% of people with claims for low dose quetiapine had an evidence-supported diagnosis in the 6 months before the first claim in the reporting period. The most common diagnoses included major depressive disorder (45%), generalized anxiety disorder (26%), bipolar disorder (26%), and schizophrenia (3%).
- About 5.5% of patients had a diagnosis indicating sleep disorders in the absence of another evidence-supported indication.

- Compared to people with diagnoses of bipolar disorder and schizophrenia, denied claims were more common for members with major depressive disorder and generalized anxiety disorder. Of members with denied claims, most had diagnoses for major depressive disorder (24%), generalized anxiety disorder (20%), or no evidence-supported diagnosis (58%).

Use of other mental health medications

- Members with claims for low dose quetiapine were commonly prescribed antipsychotics (76%), selective serotonin-reuptake inhibitors (SSRI) or serotonin norepinephrine-reuptake inhibitors (SNRI) (52%), other antidepressants (35%) and benzodiazepines (22%) in the 6 months prior to the first claim for low dose quetiapine in the reporting period.
- Nearly all patients (more than 99%) with an initial paid for low dose quetiapine had other paid claims for antipsychotics in the previous 6 months.
- Denied claims were more common for members with recent claims for an SSRI/SNRI or with no other prior claims for mental health drugs.
    - About 40% of members with denied claims had a recent claim for an SSRI or SNRI.
    - About 38% of members with denied claims had no prior claims for antidepressants, antipsychotics, benzodiazepines, or other bipolar medications.

Access to mental health prescribers

- Only 36% of members had low dose quetiapine prescribed by a mental health provider.

Recommendations:

- Update PA criteria for low dose quetiapine to incorporate GAD (**Appendix 2**).
- Automatically approve PA requests for extended-release quetiapine in members with recent claims for an SSRI or SNRI.

Background:

Quetiapine is a second generation antipsychotic which is been approved by the Food and Drug Administration (FDA) for bipolar disorder, schizophrenia and as adjunct treatment for depression.[1,2] Initial doses for someone starting therapy are as low as 50 mg daily and recommended doses range from 150 to 800 mg daily depending on the indication.[1] When starting treatment, dose adjustments can be made daily, and titration to the minimum recommended maintenance dose can be achieved within 2 to 5 days.[1] Low dose quetiapine (<150 mg) may be used off-label for a variety of conditions including insomnia, anxiety, obsessive compulsive disorder and dementia.[2] Because of significant safety concerns associated with long-term use and lack of evidence supporting efficacy, quetiapine is not recommended by current guidelines for treatment of insomnia. Quetiapine has also been associated with significant safety concerns including increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behaviors in children and adolescents.[1,2] Adverse effects documented with quetiapine also include:[1,2]

- metabolic changes such as hyperglycemia, dyslipidemia, and weight gain;
- changes in thyroid hormones and prolactin levels;
- changes in blood pressure and increased risk of falls;
- extrapyramidal symptoms and tardive dyskinesia;
- anticholinergic effects such as urinary retention, sedation, and constipation; and
- development of cataracts with long-term use.

However, recent algorithms from the Mental Health Clinical Advisory Group document note that quetiapine extended-release tablets may have benefit when used as adjunctive to an SSRI or SNRI for adults with generalized anxiety disorder who have failed to have benefit with multiple trials of SSRI or SNRI monotherapy. Consultation with a mental health provider is recommended when considering adjunct use of quetiapine for generalized anxiety disorder.

Previous drug use evaluations documented that most Medicaid members without an FDA-approved diagnosis present in medical claims were prescribed quetiapine at a dose of less than or equal to 50 mg daily. Currently, prescriptions for low dose quetiapine (≤50 mg daily) require prior authorization (PA) to discourage off-label use for sleep conditions for which risks outweigh benefits. Patients with diagnoses of schizophrenia, bipolar disorder, history of use for a second-generation antipsychotic, or prescriptions written by a mental health specialist can be automatically approved. This drug use evaluation examines utilization patterns with the current low dose quetiapine safety edit and explores how criteria could be modified to minimize administrative barriers for appropriate populations.

Methods:

Patients were identified for inclusion based on paid or denied FFS claims for quetiapine (First Databank HICL sequence number [HSN] 014015). The evaluation window for quetiapine claims was from 7/1/2021 to 06/30/2022. The index event (IE) was defined as the first paid or denied claim for quetiapine in the evaluation window. For each patient, the baseline and follow-up periods were defined based on the IE.

- The baseline period was defined as the 6 months prior to the IE (exclusive of the IE).
- The follow-up period was defined as the 3 months after the IE (inclusive of the IE)

Patients were categorized into the following groups based on the IE and claims for quetiapine in the follow-up period:

(1) patients with a claim that was initially paid or paid within one day of the IE (i.e., the day after the IE).
(2) patients with denied claims where there was a subsequent claim paid within 2-90 days following the IE or where there was no subsequent paid claim in the following 90 days.

Inclusion criteria:

- At least one paid or denied FFS claims for quetiapine during the evaluation window. Denied claims were included if they were associated with error codes of 3002 “NDC requires PA” or 3000 “units exceed authorized units on PA master file” without any of the error codes listed in **Appendix 1**.

Exclusion criteria:

- Patients with daily dose greater than 50 mg on the IE. Any claims for the dose pack (First Databank generic sequence number [GSN] 074076), which includes tablets of multiple strengths and is commonly used for titration, were classified according to the highest dose tablet (300 mg per tablet).
- Patients with Medicare part D coverage or limited or no Medicaid drug benefit in the baseline period

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

- Patients with primary insurance coverage (i.e., third party liability [TPL]) in the baseline period
- Patients with non-continuous Medicaid enrollment in the baseline period
- Patients with non-continuous Medicaid enrollment in the follow-up period

Outcomes:

- Proportion of patients have an evidence-supported diagnosis for schizophrenia, bipolar disorders, major depressive disorder, or generalized anxiety disorder based on medical claims in the baseline period (**Appendix 1**).
- Proportion of patients who have paid claims (CCO or FFS) for other mental health drugs in the baseline period.
- Proportion of patients who have paid claims (CCO or FFS) for long-term therapy with mental health drugs (>90 covered days) in the baseline period
- Proportion of patients who have the IE prescribed by a mental health provider (identified by primary taxonomy listed in **Appendix 1)**.

Results:

Table 1. Included patients

Number of included patients	#	%
Paid or denied FFS claim for quetiapine from 7/1/2021 to 06/30/2022	**13,043**	
After exclusion of IE with > 50 mg daily	5,053	38.7%
After exclusion of Medicare part D, limited benefit plans, and TPL	4,810	36.9%
After exclusion of non-continuous Medicaid enrollment in the baseline period	4,291	32.9%
After exclusion of non-continuous Medicaid enrollment in the follow-up period	**4,226**	32.4%

Table 2 includes demographics and basic drug information for people with paid or denied claims for low dose quetiapine. A total of 4226 people were included in this analysis and accounted for about 32% of people with claims for quetiapine. Of these patients, about 76% of members had an initial paid claim or claim paid within one day of an initial denial and 24% of members had a denied claim. About 63% of members were female, and almost 86% were adults 18 to 59 years of age. Five percent of claims were for children or adolescents less than 18 years of age. Immediate-release formulations of quetiapine accounted for 96% of initial claims. The dose per day for the first claim in the evaluation window was 26 to 50 mg per day for about 63% of members. Denied claims were slightly more common for members with doses lower than 25 mg daily. About 58% of members identified as white, 26% did not identify race to Medicaid, 7% identified as American Indian/Alaskan Native, and 9% included other racial groups.

Table 2. Demographics at the time of the IE

	Paid Claim (OR paid within 1 day)		**Initial Denied Claim**		**Total**	
	3,216	**76.1%**	**1,010**	**23.9%**	**4,226**	**%**
Female	2,082	64.7%	590	58.4%	2,672	63.2%
Age – mean (range)	38	(5-94)	38	(7-91)	38	(5-94)
0-9	13	0.4%	7	0.7%	20	0.5%
10-17	179	5.6%	34	3.4%	213	5.0%
18-59	2,758	85.8%	873	86.4%	3,631	85.9%
>=60	266	8.3%	96	9.5%	362	8.6%

Dose						
<=25 mg/day	1,077	33.5%	**479**	**47.4%**	**1,556**	**36.8%**
26-50 mg/day	2,139	66.5%	531	52.6%	2,670	63.2%
Race						
White	1,879	58.4%	568	56.2%	2,447	57.9%
American Indian/Alaskan Native	220	6.8%	82	8.1%	302	7.1%
Other	269	8.4%	97	9.6%	482	8.7%
Unknown	848	26.4%	263	26.0%	995	26.3%
Formulation						
Immediate-release	3,091	96.1%	978	96.8%	4,069	96.3%
Extended-release	125	3.9%	32	3.2%	157	3.7%

About 69% of people with claims for low dose quetiapine had an evidence-supported diagnosis in the 6 months before the claim (**Table 3**). Diagnoses included 45% of members with major depressive disorder, 26% with generalized anxiety disorder, 26% with bipolar disorder, and 3% with schizophrenia. About 31% of members did not have a diagnosis supported by the evidence in the 6 months before the IE for low dose quetiapine. For people with and evidence-supported diagnosis in medical claims, almost 78% of members had an initial claim paid or paid within one day for low dose quetiapine. Initial paid claims were more common for people with diagnoses of schizophrenia and bipolar disorder (which are included in the auto-PA criteria), and denials were more common for members with diagnoses of major depressive disorder or generalized anxiety disorder. Of members with denied claims, most had diagnoses for major depressive disorder (24%), generalized anxiety disorder (20%) or no evidence-supported diagnosis (58%). Many patients had more than one diagnosis in medical claims making it difficult to determine the primary reason for the quetiapine prescription. Of the 1,010 members who had a denial, 328 (32%) had a subsequent paid claim in the 2-90 days after then initial denial (data not shown).

Diagnoses for insomnia and sleep disorders were present for only about 5% of people without an evidence-supported diagnosis. Denied claims were more common in this population, and of the 1,310 members without an evidence-supported diagnosis, and only 55% of members (n=720) had an initial paid claim.

Table 3. Diagnoses in the 6 months before the IE

	Paid claim (OR paid within 1 day)		**Initial Denied Claim**		**Total**	
	3,216	**%**	**1,010**	**%**	**4,226**	**%**
Evidence-supported diagnoses	2,496	77.6%	420	41.6%	2,916	69.0%
Major Depressive Disorder	1,671	52.0%	**240**	**23.8%**	1,911	45.2%
Generalized Anxiety Disorder	903	28.1%	**199**	**19.7%**	1,102	26.1%
* Bipolar Disorder	996	31.0%	97	9.6%	1,093	25.9%
* Schizophrenia	121	3.8%	6	0.6%	127	3.0%

None of the above (no evidence-supported diagnosis)	720	22.4%	590	58.4%	1,310	31.0%
Insomnia/circadian rhythm sleep disorders	90	2.8%	141	14.0%	231	5.5%
Dementia/delirium/Alzheimer's	25	0.8%	35	3.5%	60	1.4%
Parkinson's Disease	2	0.1%	3	0.3%	5	0.1%
Obsessive Compulsive Disorder	14	0.4%	7	0.7%	21	0.5%

*Incorporated in the auto-PA

Nearly all patients (>99%) with an initial paid claim for low dose quetiapine had paid claims for antipsychotics in the 6 months before the first claim for low dose quetiapine in the evaluation window (**Table 4**). This corresponds with the current PA policy to auto-approve requests if the member has prior history of antipsychotic use. All patients without an evidence-supported diagnosis in medical claims that had an initial paid claim for low dose quetiapine had claims for an antipsychotic in the previous 6 months. Although not included in the auto-PA, patients with history of lithium or divalproex also commonly had initial paid claims for low dose quetiapine regardless of diagnosis history. Just over half of members with claims for low dose quetiapine had claims for an SSRI/SNRI (52%). Denied claims were common in members with recent claims for an SSRI/SNRI; about 40% of members with denied claims had a recent claim for an SSRI or SNRI. A small proportion of patients (9.4%) had no recent claims for antipsychotics, antidepressants (including other antidepressants, SSRIs, or SNRIs), benzodiazepines or other bipolar disorder drugs. This group of members was likely to have denied claims and accounted for about 38% of members with denials.

To evaluate longer-term use of co-prescribed mental health medications, we examined utilization of medications dispensed for more than 90 days in the 6 months before the IE (**Table 4**). Compared to patients with any claim for other mental health drugs, a substantially smaller proportion of members had more than 90 covered days for antipsychotics (76% vs. 38%), SSRIs or SNRIs (52% vs. 37%), other antidepressants (35% vs. 22%), and benzodiazepines (22% vs. 5%). Utilization of other mental health medications is broken out by presence or absence of an evidence-supported diagnosis in **Table 5**. Utilization patterns for mental health medications were generally consistent, regardless of presence or absence of diagnoses in medical claims. Members with claims for low dose quetiapine were commonly prescribed antipsychotics or antidepressants in the previous 6 months for both populations.

Table 4. Patients with mental health medications prescribed in the 6 months before the IE

	Paid claim (OR paid within 1 day)		**Initial Denied Claims**		**Total**	
	3,216	**76.1%**	**1,010**	**23.9%**	**4,226**	**%**
Any paid claim	3,206	99.7%	622	61.6%	3,828	90.6%
* Antipsychotics (1st gen, 2nd gen, parenteral)	3,200	99.5%	11	1.1%	3,211	76.0%
Selective serotonin-reuptake inhibitors (SSRI) or serotonin norepinephrine-reuptake inhibitors (SNRI)	1,810	56.3%	400	39.6%	2,210	52.3%
Other antidepressant	1,198	37.3%	301	29.8%	1,499	35.5%
Benzodiazepine	754	23.4%	183	18.1%	937	22.2%
Bipolar Disorder drug (lithium/divalproex)	297	9.2%	21	2.1%	318	7.5%
None of the above drug classes	10	0.3%	388	38.4%	398	9.4%

Paid claims for >90 covered days	2,385	74.2%	334	33.1%	2,719	64.3%
* Antipsychotics (1st gen, 2nd gen, parenteral)	1,597	49.7%	4	0.4%	1,601	37.9%
Selective serotonin-reuptake inhibitors (SSRI) or serotonin norepinephrine-reuptake inhibitors (SNRI)	1,330	41.4%	230	22.8%	1,560	36.9%
Other antidepressant	773	24.0%	139	13.8%	912	21.6%
Benzodiazepine	208	6.5%	9	0.9%	217	5.1%
Bipolar Disorder drug (lithium/divalproex)	172	5.3%	21	2.1%	193	4.6%

*Incorporated in the auto-PA

Table 5. Patients with other therapy mental health drugs prescribed in the 6 months before the IE (any paid claim)

	Paid claim (OR paid within 1 day)		Initial Denied Claims		Total	
	3,216	**76.1%**	**1,010**	**23.9%**	**4,226**	**%**
Evidence-supported diagnoses	2,489	77.4%	287	28.4%	2,776	65.7%
* Antipsychotics (1st gen, 2nd gen, parenteral)	2,483	77.2%	7	0.7%	2,490	58.9%
Selective serotonin-reuptake inhibitors (SSRI) or serotonin norepinephrine-reuptake inhibitors (SNRI)	1,467	45.6%	202	20.0%	1,669	39.5%
Other antidepressant	990	30.8%	143	14.2%	1,133	26.8%
Benzodiazepine	636	19.8%	84	8.3%	720	17.0%
Bipolar Disorder Drug (lithium/divalproex)	249	7.7%	5	0.5%	254	6.0%
None of the above drug classes	7	0.2%	133	13.2%	140	3.3%
None of the above (no evidence-supported diagnosis)	717	22.3%	335	33.2%	1,052	24.9%
* Antipsychotics (1st gen, 2nd gen, parenteral)	717	22.3%	4	0.4%	721	17.1%
Selective serotonin-reuptake inhibitors (SSRI) or serotonin norepinephrine-reuptake inhibitors (SNRI)	343	10.7%	198	19.6%	541	12.8%
Other antidepressant	208	6.5%	158	15.6%	366	8.7%
Benzodiazepine	118	3.7%	99	9.8%	217	5.1%
Bipolar Disorder drug (lithium/divalproex)	48	1.5%	16	1.6%	64	1.5%
None of the above drug classes	3	0.1%	255	25.2%	258	6.1%

*Incorporated in the auto-PA

Only 36% of members had prescriptions written by a mental health specialist. However, members with a prescription written by a mental health specialist more commonly had an initial paid claim compared to members with prescriptions from other prescriber types.

Table 6. Provider taxonomy on the index event

	Paid claim (OR paid within 1 day)		Initial Denied Claims		Total	
	3,216	%	1,010	%	4,226	%
Evidence-supported diagnoses						
Mental health provider	1,180	36.7%	20	2.0%	1,200	28.4%
Other	1,316	40.9%	400	39.6%	1,716	40.6%
None of the above (no evidence-supported diagnosis)						
Mental health provider	302	9.4%	25	2.5%	327	7.7%
Other	418	13.0%	565	55.9%	983	23.3%

Limitations and Discussion

Claims-based analyses have several inherent limitations including:

- Diagnostic data based on claims history may be incomplete or not accurately reflect true patient diagnoses. Social stigma associated with mental health conditions (from patients or providers) may result in incomplete or missing diagnoses billed on medical claims. Diagnostic data was evaluated only over a 6-month period, and diagnoses for patients on stable maintenance therapy may be missed if they had infrequent provider visits. Additionally, many members included in this analysis had more than one diagnosis in medical claims which makes it difficult to attribute prescription of quetiapine to a specific diagnosis. While the current policy for quetiapine does not explicitly allow coverage of quetiapine for generalized anxiety disorder, some members with this diagnosis did have paid claims for quetiapine. This could be due to multiple factors including:
    - Prescription of quetiapine by a mental health specialist
    - Comorbid diagnosis for a covered condition (such as schizophrenia or bipolar disorder)
    - Paid claims for an antipsychotic in the previous 6 months
- Provider type may be inaccurate or incomplete. Providers with a mental health specialty were identified based on primary prescriber taxonomy which may not accurately reflect their actual practice setting. For example, physician assistants working under the supervision of a mental health specialist may be categorized as a general practitioner. Additionally, it is unknown what proportion of general practitioners have consulted a mental health provider before prescribing low dose quetiapine.
- Utilization data of other mental health drugs, which are based on pharmacy claims, may not actually reflect true utilization or may be incomplete. This analysis uses paid pharmacy claims as a surrogate marker for utilization, but this may not reflect how the member actually takes the drug. Many mental health medications are available as generics and are relatively inexpensive. Some patients who encounter barriers to coverage may elect to pay cash for their prescriptions. The extent of patients who pay cash for prescriptions is unknown, and these prescriptions would not be captured in this analysis.
- Of note, almost all members with an initial paid claim for low dose quetiapine had utilization for an antipsychotic in the prior 6 months. Several factors may contribute to this:

- Pharmacy claims are adjudicated in real-time whereas medical claims take longer to adjudicate before they are available in the claims processing system. Therefore, pharmacy data may be a more consistent trigger for the autoPA (compared to diagnostic data from medical claims).
- This analysis was limited to members who were continuously enrolled with Medicaid for a 9 month period (6 months before the IE and 3 months after the IE). Over 800 people (about 15%) were eliminated from the analysis because of these eligibility requirements. This methodology may select for members with more severe mental health conditions and comorbidities who are more likely to have received prior prescriptions for an antipsychotic.

References:

1. Seroquel XR (quetiapine) extended-release tablets [package labeling]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2022.
2. Quetiapine In: Merative Micromedex® Alternative Medicine (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: April 30, 2023).

Appendix 1. Drug Coding

Table A1. Quetiapine GSN codes

GSN	Form	Generic	Type
034187	TABLET	quetiapine fumarate	Immediate-release
034188	TABLET	quetiapine fumarate	Immediate-release
034189	TABLET	quetiapine fumarate	Immediate-release
043198	TABLET	quetiapine fumarate	Immediate-release
047198	TABLET	quetiapine fumarate	Immediate-release
060292	TABLET	quetiapine fumarate	Immediate-release
060293	TABLET	quetiapine fumarate	Immediate-release
062748	TAB ER 24H	quetiapine fumarate	Extended-release
062749	TAB ER 24H	quetiapine fumarate	Extended-release
062750	TAB ER 24H	quetiapine fumarate	Extended-release
063240	TAB ER 24H	quetiapine fumarate	Extended-release
064725	TAB ER 24H	quetiapine fumarate	Extended-release
074076	TAB24HDSPK	quetiapine fumarate	Extended-release

Table A2. Diagnosis codes

Condition	ICD-10 Diagnosis Code
Schizophrenia	F20x
Bipolar Disorders	F31x
MDD	F322-F323, F329; F33x
GAD	F411x
Dementia/delirium/Alzheimer's Disease	F01x-F05x, G30x
Parkinson's Disease	G20x
Obsessive Compulsive Disorder (OCD)	F42x
Insomnia or circadian rhythm sleep disorders	G470x, G472x

Table A3. Error Codes associated with denied claims that are excluded from the analysis

Error Code	Description
4999	THIS DRUG IS COVERED BY MEDICARE PART D
2508	RECIPIENT COVERED BY PRIVATE INSURANCE (PHARMACY)
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
2507	RECIPIENT HAS MORE THAN ONE INSURANCE CARRIER
513	RECIPIENT NAME AND NUMBER DISAGREE
503	DATE DISPENSED AFTER BILLING DATE
628	Other Coverage Reject Code Required for OCC 3
205	PRESCRIBING PROVIDER ID MISSING
502	DATE DISPENSED EARLIER THAN DATE PRESCRIBED
214	DATE PRESCRIBED IS INVALID
268	BILLED AMOUNT MISSING
271	HEADER TOTAL BILLED AMOUNT INVALID
269	DETAIL BILLED AMOUNT INVALID
500	DATE PRESCRIBED AFTER BILLING DATE
222	DAYS SUPPLY INVALID
221	DAYS SUPPLY MISSING
238	RECIPIENT NAME IS MISSING
1040	PRESCRIBING PHYSICIAN NOT ENROLLED
1026	PRESCRIBING PHYSICIAN ID NOT ON FILE

Table A4. Taxonomy codes associated with mental health providers

Taxonomy	Taxonomy Description
163WP0807X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
163WP0808X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
163WP0809X	REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH
167G00000X	NURSING SERVICE - LICENSED PSYCHIATRIC TECHNICIAN
2080P0008X	PHYSICIAN-PEDIATRICS-NEURODEVELOPMENTAL DISABILITIES
2084A0401X	PSYCHIATRY & NEUROLOGY, ADDICTION MEDICINE
2084B0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-BARIATRIC MEDICINE
2084B0040X	BEHAVIORAL NEUROLOGY & NEUROPSYCHIATRY
2084D0003X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-DIAGNOSTIC NEUROIMAGING
2084F0202X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY
2084H0002X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-HOSPICE AND PALLIATIVE MEDICINE
2084N0008X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROMUSCULAR MEDICINE
2084N0400X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY
2084N0402X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO

2084N0600X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-CLINICAL NEUROPHYSIOLOGY
2084P0005X	PHYSICIAN-PSYCHIATRY&NERUOLOGY-NEURODEVELOPMENTAL DISABILITIES
2084P0015X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHOSOMATIC MEDICINE
2084P0800X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY
2084P0802X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-ADDICTION PSYCHIATRY
2084P0804X	PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY
2084P0805X	PHYSICIAN-PSYCHIATRY&NEUROLGY-GERIATRIC PSYCHIATRY
2084P2900X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-PAIN MEDICINE
2084S0010X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SPORTS MEDICINE
2084S0012X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-SLEEP MEDICINE
2084V0102X	PHYSICIAN-PSYCHIATRY&NEUROLOGY-VASCULAR NEUROLOGY
261QM0850X	CLINIC/CENTER - ADULT MENTAL HEALTH
273R00000X	PSYCHIATRIC UNIT
283Q00000X	HOSPITALS: PSYCHIATRIC HOSPITAL
3104A0625X	NURSING&CUSTODIAL CARE: ASSISTED LIVING - MENTAL ILLNESS
3104A0630X	NURSING&CUSTODIAL CARE: ASSISTED LIVING - BEHAVIORAL DISTURBANCES
310500000X	NURSING&CUSTODIAL CARE: ASSISTED LIVING - MENTAL ILLNESS
311500000X	NURSING&CUSTODIAL CARE: ALZHEIMER CENTER (DEMENTIA CENTER)
323P00000X	PSYCHIATRIC RESIDENTIAL TREATMENT FACILITY
363LP0808X	NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH
364SP0807X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0808X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0809X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0810X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0811X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0812X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH
364SP0813X	CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH

Table A. Drug definitions for other mental health drugs

Drug Category	PDL Class or generic drug name	HSN
Antipsychotics (by PDL class)	Antipsychotics, 2nd gen Antipsychotics, 1st gen Antipsychotics, parenteral	N/A
Benzodiazepines (by PDL class)	Benzodiazepines	N/A
Bipolar Drugs (by HSN)	Lithium carbonate	001669
	Valproic acid as sodium salt	001882

	Valproic acid	001883
	Divalproex sodium	001884
SSRI/SNRIs (by HSN)	desvenlafaxine	040202
	desvenlafaxine succinate	035420
	duloxetine HCl	026521
	levomilnacipran HCl	040632
	venlafaxine besylate	048091
	venlafaxine HCl	008847
	citalopram hydrobromide	010321
	escitalopram oxalate	024022
	fluoxetine HCl	001655
	fluvoxamine maleate	006338
	paroxetine HCl	007344
	paroxetine mesylate	025796
	sertraline HCl	006324
	olanzapine/fluoxetine HCl	025800
	vilazodone HCl	037597
	vortioxetine hydrobromide	040637
Other antidepressants (by HSN)	brexanolone	045692
	selegiline	033510
	amitriptyline HCl	001643
	amoxapine	001648
	clomipramine HCl	004744
	desipramine HCl	001645
	doxepin HCl	001650
	imipramine HCl	001641
	imipramine pamoate	001642
	maprotiline HCl	001651
	nortriptyline HCl	001644
	protriptyline HCl	001646
	trimipramine maleate	001649
	mirtazapine	011505
	bupropion HBr	036156
	bupropion HCl	001653
	nefazodone HCl	009612
	trazodone HCl	001652
	isocarboxazid	001638

	phenelzine sulfate	001639
	tranylcypromine sulfate	001640
	esketamine HCl	041003

Appendix 2. Proposed Safety Edit

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine, immediate- and extended-release~~(Seroquel® and Seroquel XR®)~~

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto-PA approvals for:
  - Patients with a claim for a second-generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider
  - Extended-release formulations in patients with claims for a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor in the last 90 days

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Table 1. Adults (age ≥18 years) with FDA-approved or Compendia-supported Indications ~~for Quetiapine~~

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	

Generalized Anxiety Disorder (GAD)	Adjunctive therapy with SSRI/SNRI

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Note: For any requests in children ≤5 years of age, see criteria for Antipsychotics in Children

Approval Criteria		
1. Is the request for an evidence-supported diagnosis (Table 1 or Table 2)?~~What diagnosis is being treated?~~	**Yes:** Go to #2~~Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)~~	No: Pass to RPh. Deny; medical appropriateness.
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy (at ≤50 mg) longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? ~~any diagnosis in table 1 or 2 above?~~	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *4/21 (SF); 8/20; 3/19; 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

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New Drug Evaluation: Omaveloxolone Oral Capsules

Date of Review: June 2023
Generic Name: Omaveloxolone

End Date of Literature Search: 03/09/23
Brand Name (Manufacturer): Skyclarys™ (Reata Pharmaceuticals, Inc.)

Dossier Received: yes

Plain Language Summary:

- This review looks at evidence for the safety and effectiveness of omaveloxolone oral capsules. Omaveloxolone is the first medicine approved in the United States to treat a condition known as Friedrich's ataxia.
- Friedreich's ataxia is a rare, inherited disease that causes damage to the nervous system and decreases the length of life of people with this condition. People with Friedreich's ataxia usually start to have symptoms in childhood or as young adults. People with Friedreich's ataxia have unsteady balance, muscle weakness and it becomes harder to walk, dress, and speak as time goes on. The main goals of therapy are to treat the symptoms and provide support. Until recently, there were no medicines approved to treat this condition.
- Omaveloxolone improved coordination in people with Friedrich's ataxia in a single 48-week study.
- Omaveloxolone may increase liver function tests. These changes in test results were temporary and returned to normal when omaveloxolone was discontinued. Other side effects seen from people in the study were nausea, headache, stomach pain, diarrhea, and feeling tired.
- Providers who prescribe omaveloxolone to a person enrolled in the Oregon Health Plan must explain to the Oregon Health Authority why someone needs omaveloxolone before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

- What is the evidence for the efficacy of omaveloxolone for treatment of Friedrich's ataxia in adults and adolescents?
- What are the harms associated with the use of omaveloxolone?
- Are there specific populations or communities, based on demographic characteristics, who would be more likely to benefit or be harmed from the use of omaveloxolone?

Conclusions:

- Omaveloxolone is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.[1] Omaveloxolone oral capsules received Food and Drug Administration (FDA) approval in February 2023 with priority review under orphan drug status and rare pediatric disease designation.[2] The efficacy and safety of omaveloxolone to treat Friedreich's ataxia were evaluated in a multi-center, placebo-controlled, double-blind, Phase 2 randomized trial (MOXIe).[2,3]

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- In the MOXIe study, 103 patients were randomized 1:1 to omaveloxolone 150 mg once a day (n=51) or placebo (n=52) for 48 weeks to evaluate safety and efficacy of omaveloxolone.[2] The primary analysis was the change from baseline in the modified Friedreich's Ataxia Rating Scale (mFAR) score for people who received omaveloxolone compared to placebo after 48 weeks of treatment in the full analysis population of patients (n=82).[2] The minimum score for the mFARS is 0 and the maximum score is 99.[2] A lower score indicates better neurological function and less physical impairment.[2] Improvement was defined by the investigators was an increase of no more than 1.9 points in mFAR score from baseline.[2] At 48 weeks, low quality-evidence showed mean mFAR scores (scale 0-99) improved by 1.55 points in the omaveloxolone group and worsened by 0.85 points in the placebo group (mean difference between groups -2.4 points; 95% confidence interval [CI] -4.3 to -0.5; p=0.014).[2] The clinical significance of this difference for a 99-point scale is unclear.
- The most common adverse effects of omaveloxolone observed in clinical trials were transient increases in alanine transaminase (ALT) and aspartate aminotransferase (AST), headache, nausea, abdominal pain, fatigue, diarrhea and musculoskeletal pain.[1] In part 2 of the MOXIe trial, increases in BNP above the upper limit of normal (100 pg/mL) were observed in 14% of omaveloxolone-treated patients (compared with 4% of placebo-treated patients).[2] The manufacturer recommends obtaining ALT, AST, bilirubin, B-type natriuretic peptide (BNP), and lipid parameters prior to initiating treatment and periodically during treatment.[1]
- Omaveloxolone is contraindicated in patients with severe hepatic impairment. In patients with moderate hepatic impairment the omaveloxolone dose should be adjusted to 100 mg once daily.[1] Due its hepatic metabolism by CYP3A4 enzymes, there are numerous drug interactions between omaveloxolone and other medications. The omaveloxolone dose should be adjusted to 50 or 100 mg once daily when co-administered with strong or moderate CYP3A4 inhibitors, respectively.[1]
- Ninety-seven percent of study participants in the MOXIe study were white,[2] non-white populations were not represented in the study; this undermines confidence in this evidence applies communities served by OHP.

Recommendation:

- Maintain omaveloxolone as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) with clinical prior authorization (PA) criteria to ensure medically appropriate use.

Background:

Friedreich's ataxia, is a rare, progressive, autosomal recessive, neurodegenerative disorder. It is the most common hereditary ataxia in people of Western European descent.[4] The estimated prevalence of Friedreich's ataxia in European populations is 1 in 50,000.[5] In the United States, prevalence is approximately 5,000 people.[2] The prevalence of this condition is lowest in China, Japan, and sub-Saharan Africa.[4] Within the Oregon Health Plan (OHP), 30 people enrolled during 2022 have Friedreich's ataxia, with most of these people receiving care in through a coordinated care organization (CCO).

Friedreich's ataxia is associated with mutations in the frataxin gene located on chromosome 9q13, which leads to impaired transcription of the protein, frataxin.[6] Patients with Friedrich's ataxia have expanded guanine-adenine-adenine (GAA) trinucleotide repeats of both alleles of the frataxin gene.[6] In Friedrich's ataxia, the number of GAA repeats can vary from 66 to 1700, compared with 7 to 34 in a normal allele.[5] The larger expansions of GAA repeats are associated with increased severity of this condition.[6] Frataxin is essential for normal mitochondrial function and adenosine triphosphate (ATP) production.[6] Frataxin deficiency is associated with abnormal accumulation of intramitochondrial iron, defective mitochondrial respiration, and overproduction of oxygen free radicals, causing cell damage.[2,4] Studies have also demonstrated that nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) signaling is impaired in patients with Friedreich's ataxia.[2] In healthy people, oxidative stress causes Nrf2 to increase the expression of antioxidant genes, which protect cells from damage.[2] The recently approved treatment for Friedrich's ataxia, omaveloxolone, is an activator of Nrf2 signaling.[2]

Friedreich's ataxia presents as impaired coordination of both arms and legs, loss of normal reflexes in the ankles and knees, vision and hearing loss, slurred speech, scoliosis, and increased spasticity.[5] The onset of symptoms is usually before 20 years of age, and the symptoms will continue to progress with increasing difficulty in balance, gait, and activities of daily living (i.e., writing, dressing, washing and feeding).[5] Age of onset is an important predictor of disease severity and the speed of disease progression.[7] Children diagnosed with early onset Friedreich ataxia before 7 years of age tend to have more genetic mutations and severe symptoms that rapidly progress to impaired neuromuscular abilities.[7] Skeletal deformities and cardiomyopathy are found in a majority of patients, who also have an increased frequency of impaired glucose tolerance and diabetes.[5] Most early-onset patients will be wheel-chair dependent by their late teens or early twenties.[5] The mean age of death is 37.5 years, although some patients with late-onset ataxia (after 25 years of age) have survived until they reached 80 years of age.[4] The major cause of death is congestive heart failure or cardiac arrhythmia.[8,9]

The diagnosis of Friedrich's ataxia is based upon clinical findings and confirmed by genetic testing.[4] Neuroimaging of the brain and spinal cord is recommended to exclude other causes of ataxia.[4] The neurological-exam-based Friedreich's Ataxia Rating Scale (FARS) was developed to assess the severity of ataxia symptoms.[10] The maximum score is 125 points based five sections that measure: bulbar function (score 0 to 11); upper limb coordination (score 0 to 36); lower limb coordination (score 0 to 16); peripheral nervous system function (score 0 to 26) and upright stability (score 0 to 36).[10,11] The interrater reliability of this tool was verified in 3 studies of patients with Friedreich's ataxia.[12-14] However, the minimal clinically important difference (MCID) for this assessment was never defined.[14] An assessment of the ability to complete activities of daily living (ADL) is part of the FAR scoring.[10] The FARS-ADL is a 9-question assessment which assesses 9 abilities: speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function.[10] Each component is scored between 0 and 4, with 0 being normal and 4 being worst.[10]

The modified FARS (mFARS) is another clinical assessment tool used to assess patient function and includes 4 of the 5 sections of the FARS: bulbar function, upper limb coordination, lower limb coordination, and upright stability.[2] Peripheral nervous system function is not measured in the mFAR scoring. The minimum score is 0 and the maximum score is 99.[2] A lower score indicates better neurological function and less physical impairment.[2] A reduction in FARS or mFARs signifies improved functioning.[10] An MCID for the mFARS has also not been determined. However, in a 5-year natural history study that included over 800 patients aged 4 to 80 years with Friedreich's ataxia, the mean progression in mFARS scores from baseline was 1.9 points by year one, 4.2 points by year 2, and 9.6 points by year 5.[13]

Management of Friedrich's ataxia is palliative and focused on symptomatic support from physical therapy, cardiology, endocrinology, neurology, and orthopedics to maintain optimal functioning as long as possible.[4] Until the recent FDA-approval of omaveloxolone, no medication has been approved to treat Friedrich's ataxia. Several ongoing investigational studies with antioxidants and gene therapy are assessing additional pathways besides Nrf2 signaling to treat Friedrich's ataxia and include targeting mitochondrial function or frataxin expression.[15]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Omaveloxolone is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.[1] Omaveloxolone oral capsules received FDA approval in February 2023 with priority review with orphan drug status and rare pediatric disease designation.[2] Omaveloxolone is an activator of nuclear factor (erythroid-derived 2) related factor signaling, which is involved in the cellular response to oxidative stress.[1] The recommended dose is 150 mg (3 capsules) once daily at least one hour before eating.[1]

The efficacy and safety of omaveloxolone to treat Friedreich's ataxia was evaluated in a 2-part, multi-center, placebo-controlled, double-blind, Phase 2 RCT (MOXIe).[2,3] The first part of this study was a 12-week dose escalation assessment in which various oral omaveloxolone doses ranging from 2.5 mg to 300 mg or placebo were administered to enrolled patients (n=69). Patients were split into 9 cohorts and randomized 3:1 to omaveloxolone (n=6) or placebo (n=2) at the specified dose for each cohort.[3] The primary efficacy outcome was change in peak work achieved during cardiopulmonary exercise testing on a stationary bicycle. No significant changes were observed in this endpoint, but improvements in the mFAR score were observed in a dose-dependent manner.[3] Patients treated with omaveloxolone 160 mg (n=4) demonstrated an improved mFAR score of 3.8 points from baseline ($p<0.001$) and a 2.3 point improvement in mFARS compared to patients taking placebo (n= 7; p=0.06) at 12 weeks.[3] The study was not powered to provide reliable results of efficacy.[10] Transaminase levels increased in a dose-dependent manner as well.[3] These increases were transient and no clinical evidence of hepatic injury was observed.[3]

In the second part of the study, 103 patients were randomized 1:1 to omaveloxolone 150 mg once a day (n=51) or placebo (n=52) for 48 weeks to evaluate safety and efficacy of omaveloxolone.[2] Because the drug is manufactured in 50 mg capsules, 150 mg was selected as the active comparator dose for ease of administration.[16] Enrolled patients were 16 to 40 years of age with genetically confirmed Friedreich's ataxia, a stable mFAR score between 20 and 80, able to swallow pills, and were able to complete maximal exercise testing on a recumbent stationary bicycle. These mFAR scores represented individuals just after time of presentation with Friedrich's ataxia in its mildest form and progression several years after loss of ambulation in a more severe form of Friedrich's ataxia.[2] Most of the patients (92%) were ambulatory. Patients with uncontrolled diabetes (HbA1c > 11%), significant cardiac disease (i.e., left-sided heart disease), active infection, clinically significant hepatic disease, and significant laboratory abnormalities (e.g., BNP > 200 pg/mL) were excluded from the study.[2] However, if patients developed diabetes or cardiac disease (i.e., arrythmias) during the trial, they were permitted to remain in the study.[2]

Patient with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight bearing, may represent a subtype of Friedrich's ataxia. Presence of pes cavus may affect people's ability to use their legs, walk, and perform neurologic testing independent of their ataxia.[10] Patients with pes cavus were limited to 20% of the total study enrollment due to possible phenotypic differences.[2] Randomization was stratified by status of pes cavus (with pes cavus or without pes cavus).[2] In this RCT, 53% of enrolled patients were male, 97% were White, and the mean age was 24 years at study entry.[2] Baseline characteristics were slightly unbalanced between groups. Compared with the placebo cohort, the omaveloxolone cohort had patients with higher baseline mFAR scores, longer GAA repeat lengths and more advanced cardiac disease.[2]

The primary analysis was the change from baseline in the mFAR score for people who received omaveloxolone compared to placebo after 48 weeks of treatment in the full analysis population of patients (n=82) without pes cavus.[2] Previous studies have shown that patients with Friedrich's ataxia, on average, decline 1 to 2 points on the FAR clinical rating scale per year.[17] Based on these studies, improvement was defined by the investigators was a change in baseline mFAR score of 1.9 points or less.[2] At 48 weeks, low quality-evidence showed mean mFAR scores improved by 1.55 points from baseline in the omaveloxolone group and worsened by 0.85 points in the placebo group (mean difference between groups -2.4 points; 95% CI -4.3 to -0.5; p=0.014).[2] Omaveloxolone-treated patients had improvement from baseline in mFAR score by week 24 (mean change, -1.66; 95% CI not reported; p=0.0191). The investigators did not present statistical data for changes from baseline in the placebo group.

Secondary endpoints included change from baseline in Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), 9-hole peg test (assessment of hand coordination), 25-foot walk test, frequency of falls, work during maximal exercise testing, and FAR-ADL Score at 48 weeks.[2] The PGIC and CGIC are 7-point scales that assess improvement or worsening in symptoms from baseline.[10] Higher scores indicate worsening symptoms.[10] The key secondary endpoints PGIC and CGIC did not reach statistical significance in the full analysis population (p=0.13; p=0.53, respectively).[10] Secondary outcomes were analyzed in prespecified order as long as statistical evidence of benefit was continued to be shown.[10] No statistically significant changes between treatment groups were

noted in any of the other secondary outcomes except for the overall FAR-ADL score (placebo = 1.14 vs. omaveloxolone = -0.17; difference = -1.30; 95% CI not reported; p=0.042).[2] Very small improvements were observed in speech, swallowing, cutting food, personal hygiene, dressing, quality of sitting position, and walking in the omaveloxolone arm compared with placebo.[10] Falling and bladder function showed less worsening in the omaveloxolone arm compared to placebo arm.[10] None of the individual components showed statistically significant treatment differences between groups except for quality of sitting position (p=0.005).[10]

Limitations of this study include small sample size, modest duration for a life-long progressive disease, and possible limitations of the generalizability of the results (see **Table 4**).[2] The study endpoints were assessed individuals who could perform an exercise test and almost all patients were ambulatory (92%).[2] It is not clear how this medication would impact patients with severe Friedreich's ataxia that are unable to walk. The MOXIe trial excluded people under the age of 16 years. As a disease that is diagnosed in children in adolescents, data regarding the safety and efficacy in this population are clinically important. Although the trial had limitations and the effect size was relatively modest, Friedreich's ataxia is a slowly progressive disease, and small differences in functional progression over 1 to 2 years could translate to meaningful differences over the course of the disease.[2]

More data are needed from long term trials to evaluate sustainability of effect on neurologic improvement and adverse effects. An open-label, non-inferiority, 72-week extension study assessed the safety and tolerability of omaveloxolone in 149 patients who were enrolled in MOXIe Part 1 or Part 2.[10,18] Of these patients, 24 (16%) discontinued the open-label study and 125 (73%) completed the study.[10] The noninferiority testing demonstrated that the difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXIe part 2 (−2.17 ± 1.09 points) was preserved after 72 weeks in the extension (−2.91 ± 1.44 points).[18] The longer-term safety profile of omaveloxolone in the extension study was similar to that seen in MOXIe Parts 1 and 2, and omaveloxolone was generally well tolerated in the extension study.[18] No deaths were reported.[18] Serious adverse events were reported in 13 (8.7%) patients; of these, 8 (7.5%) individuals were in the placebo-omaveloxolone group and 5 (11.6%) were in the omaveloxolone-omaveloxolone group.[18] All of the serious adverse events were considered by the investigator to be unrelated to study drug, and none resulted in permanent discontinuation of study drug.[18]

Specific details from Part 2 of the MOXIe trial which contribute to the safety and efficacy data for Friedreich's ataxia are described and evaluated below in **Table 4**.

Clinical Safety:
The most common adverse effects of omaveloxolone observed in Phase 1 and Phase 2 clinical trials were transient increases in ALT (maximum increase was 2 times the upper limit of normal in 16% of patients), and AST (maximum increase was 5 times the upper limit of normal in 31% of patients), headache, nausea, abdominal pain, fatigue, diarrhea and musculoskeletal pain.[1] When the drug was discontinued, ALT and AST returned to normal values within 4 weeks and no cases of sustained hepatic injury were reported.[2] In part 2 of the MOXIe trial, increases in BNP above the upper limit of normal (100 pg/mL) in 14% of omaveloxolone-treated patients (compared with 4% of placebo-treated patients) were observed.[2] Overall, mean BNP values in omaveloxolone-treated patients remained below the upper limit of normal (<100 pg/mL) , and 2 (3.8%) patients had BNP values that exceeded 200 pg/mL.[2] Twenty-nine percent of omaveloxolone-treated patients reported elevated cholesterol levels above the usual limit in part 2 of the MOXIe trial.[2] The manufacturer recommends obtaining ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating treatment and periodically during treatment.[1] Rate of adverse effects observed with omaveloxolone compared to placebo are presented in **Table 1**.

Table 1. Adverse Effects Reported in 10% or More of Patients Treated with Omaveloxolone and Greater than Placebo[1]

Adverse Effect	Omaveloxolone (n=51)	Placebo (n=52)
Elevated Liver Enzymes (ALT/AST)	37%	2%
Headache	37%	25%
Nausea	33%	13%
Abdominal Pain	29%	6%
Fatigue	24%	14%
Diarrhea	20%	10%
Musculoskeletal Pain	20%	15%
Oropharyngeal Pain	18%	6%
Influenza	16%	6%
Vomiting	16%	12%
Muscle Spasms	14%	6%
Back Pain	13%	8%
Decreased Appetite	12%	4%
Rash	10%	4%
Abbreviations: ALT = aminotransferase; AST = aspartate aminotransferase		

Omaveloxolone capsules should be taken on an empty stomach at least one hour before eating. It is important that patients prescribed omaveloxolone are able to swallow pills, as the capsules must be swallowed whole and should not be opened, crushed, or chewed.[1]

Guidance for Dosing Adjustments:

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh Class B) the omaveloxolone dose should be adjusted to 100 mg once daily.[1] If adverse effects emerge, further reduction to 50 mg once daily is recommended.[1] Omaveloxolone should not be administered to people with severe hepatic impairment (Child-Pugh Class C).[1]

Drug Interactions

- Strong CYP3A Inhibitors: Omaveloxolone maximum plasma concentration (Cmax) increased 3-fold and area under the curve (AUC) 4-fold following concomitant use with itraconazole (strong CYP3A inhibitor).[1]
- Moderate CYP3A Inhibitors: Omaveloxolone Cmax and AUC increased approximately 1.25-fold following concomitant use with verapamil (moderate CYP3A4 and P-gp inhibitor).[1]
- Strong and Moderate CYP3A Inducers: The effect of concomitant use with moderate and strong CYP3A4 inducers is unknown; however, a significant reduction in omaveloxolone exposure is likely following concomitant use based on its metabolic pathway.
- Certain CYP450 Enzymes or Transporter Substrates: omaveloxolone decreased the AUC of midazolam (CYP3A4 substrate) by approximately 45%, AUC of repaglinide (CYP2C8 substrate) by approximately 35%, and AUC of rosuvastatin (BCRP and OATP1B1 substrate) by approximately 30%.[1] There were no

clinically significant differences in the pharmacokinetics of digoxin (P-gp substrate) or metformin [(organic cation transporter (OCT)1 substrate] when co-administered with omaveloxolone.[1]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improvement in neurologic function (coordination, balance, speech)
2) Improvement in ability to complete activities of daily living
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in mFAR score from baseline at 48 weeks

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Omaveloxolone has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 pathway, which is involved in the cellular response to oxidative stress.
Oral Bioavailability	Omaveloxolone C_{max} and $AUC_{0\text{-}inf}$ increased by approximately 350% and 15%, respectively, with a high-fat meal (compared to fasted conditions).
Distribution and Protein Binding	Mean volume of distribution = 7,361 Liters and protein binding = 97%
Elimination	Primarily hepatic: 92% of a single 150 mg dose is recovered in feces
Half-Life	Mean half-life: 57 hours (range: 32 to 90 hours)
Metabolism	Primarily metabolized by CYP3A with minor metabolism by CYP2C8 and CYP2J2 hepatic enzymes

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. Lynch DR, et al.[2,10] MOXIe Study: Part 2 MC, DB, PC, PG, Phase 2 RCT	1. Omaveloxolone 150 mg orally once daily for 48 weeks 2. Placebo orally once daily for 48 weeks	Demographics: 1. Male: 53% 2. Mean age: 24 yo 3. White: 97% 4. Mean mFARS: 40 Key Inclusion Criteria: -Patients aged 16 to 40 years with genetically confirmed FA -mFARS score ≥ 20 and ≤ 80 Key Exclusion Criteria: -Uncontrolled diabetes (HbA1c > 11%) -Have a BNP > 200 pg/mL -History of significant cardiac ore hepatic disease -Taking substrates, inhibitors, or inducers of CYP3A4 or CYP2C8	ITT: 1. 51 2. 52 PP: 1. 44 2. 50 Attrition: 1. 7 (14%) 2. 2 (4%) FAS (patients without pes cavus): 1. 40 2. 42	Primary Endpoint: LSM change from baseline in mFARS score at 48 weeks in FAS 1. -1.55 +/- 0.69 2. 0.85 +/- 0.64 Difference: -2.41 95% CI -4.31 to -0.51 P=0.014 Secondary Endpoints: 1. LSM change in PGIC from baseline at 48 weeks 1. 3.89 2. 4.32 Difference: -0.4.3 P=0.13 2. LSM change in CGIC from baseline at 48 weeks 1. 3.92 2. 4.06 Difference: -0.13 P=0.53 95% CI NR 3. LSM change in performance on 9-hole peg test from baseline at 48 weeks 1. -0.0014 2. -0.0001 LSM Difference: -0.0013 P=0.18 95% CI NR 4. LSM change in performance on the 25-foot time walk test	NA NS NS NS NS	Any SAE: 1. 5 (10%) 2. 3 (6%) Discontinuation due to AE: 1. 4 (8%) 2. 2 (4%) Increased ALT: 1. 19 (37%) 2. 1 (2%) Increased AST: 1. 11 (22%) 2. 1 (2%) p-value and CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via IWRS. Small sample size may have introduced bias (103 recruited, full analysis population limited to 82 people without pes cavus). Baseline characteristics were slightly unbalanced. The omaveloxolone cohort had more advanced disease, higher baseline mFAR scores, longer GAA repeat lengths and more patients with a history of cardiomyopathy. It is not clear if patients with less advanced disease would response favorably to treatment. Performance Bias: Unclear. Study medication and placebo were identical in appearance. However, adverse effects may have resulted in unblinding. Detection Bias: Low. Sponsor, investigators, and patients were blinded to treatment assignment. Attrition Bias: High. Attrition was higher in the active treatment arm due to adverse effects and withdrawal of consent. Not clear how missing data was handled. Reporting Bias: High. Study protocol was unavailable. Secondary outcomes analyzed in prespecified order as long as statistical evidence of benefit was continued to be shown. If not significant, statistical testing was stopped. Other Bias: High. Study was sponsored and funded by drug manufacturer. Four authors are employees of the manufacturer. **Applicability**: Patient: Drug studied in FA patients with moderate impairment. Not clear how patients with severe impairment would respond to this therapy. Only studied in people aged ≥16 yo. As a pediatric condition, the role of omaveloxolone in managing FA in children is of greater interest. Non-white populations were not represented in the study; this undermines confidence in this evidence applies communities served by OHP. Intervention: 150 mg daily was the dosing approved by FDA for the FA indication. Comparator: As no other medications are approved for FA, placebo was an appropriate comparison. Outcomes: mFARs has been validated, but MCID has not been determined. Investigators relied upon historical data to determine threshold for clinical improvement.

				from baseline at 48 weeks 1. -0.0169 2. -0.0226 LSM Difference: 0.0058 P=0.46 95% CI NR 5. LSM change in frequency of falls from baseline at 48 weeks: LSM Difference: -0.32 1. 3.0 2. 8.5 P=0.28 95% CI NR 6. LSM Change in FAR-ADL from baseline at 48 weeks 1.-0.17 2. 1.14 LSM Difference: -1.30 P=0.04 95% CI NR	NS			Setting: 7 sites in US, 3 sites in Europe, and 1 site in Australia
Abbreviations AE = adverse effect; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; BNP = beta natriuretic peptide; CGIC = Clinical Global Impression of Change; CI = confidence interval; DB = double blind; FA = Friedreich's ataxia; FAR-ADL = Friedreich's Ataxia Rating-Activities of Daily Living; FAS = full-analysis set; GAA = guanine-adenine-adenine; HbA1c = hemoglobin A1c; ITT = intention to treat; IWRS = interactive web response system; MC = multi-center; MCID = minimal clinically important difference; mFARS = modified Friedreich's Ataxia Rating Scale; LSM = least squares mean; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OHP = Oregon Health Plan; PC = placebo controlled; PG = parallel group; PGIC = Patient Global Impression of Change; PO = orally; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse effect; yo = years old								

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Appendix 1: Prescribing Information Highlights

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

SKYCLARYS™ (omaveloxolone) capsules, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
SKYCLARYS is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, B-type natriuretic peptide (BNP), and lipid parameters prior to initiating SKYCLARYS and during treatment. (2.1, 5.1, 5.2, 5.3)
- Recommended dosage is 150 mg (3 capsules) taken orally once daily. (2.2)
- Administer SKYCLARYS on an empty stomach at least 1 hour before eating. (2.2)
- Swallow SKYCLARYS capsules whole. Do not open, crush or chew. (2.2)
- Moderate and Severe Hepatic Impairment: The recommended dosage of SKYCLARYS is 100 mg once daily for patients with moderate hepatic impairment. If adverse reactions emerge, further reduce the dosage to 50 mg once daily. Avoid use in patients with severe hepatic impairment. (2.5, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Elevation of Aminotransferases: Monitor ALT, AST, and total bilirubin prior to initiation, every month for the first 3 months of treatment, and periodically thereafter. (2.1, 5.1)
- Elevation of B-type Natriuretic Peptide (BNP): Advise patients of signs and symptoms of fluid overload. (2.1, 5.2)
- Lipid Abnormalities: Monitor cholesterol periodically during treatment. (2.1, 5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥20% and greater than placebo) are elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reata Pharmaceuticals, Inc. at 1-800-314-3934 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Moderate or Strong CYP3A4 Inhibitors: Avoid concomitant use. Consider SKYCLARYS dosage reduction with monitoring if use is unavoidable. (2.4, 7.1)
- Moderate or Strong CYP3A4 Inducers: Avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

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

Revised: 2/2023

Omaveloxolone (SKYCLARYS™)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling in patients with Friedreich's ataxia.

Length of Authorization:

- Up to 12 months

Requires PA:

- Omaveloxolone oral capsules (pharmacy claims)

Covered Alternatives:

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

Table 1. Recommended Dosage of Omaveloxolone with Concomitant use of CYP3A4 Inhibitors or Inducers

Concomitant Drug Class	Dosage
Strong CYP3A4 Inhibitor (such as, but not limited to: ketoconazole, nefazodone, voriconazole)	Recommended to avoid concomitant use. If co-administration cannot be avoided: • Reduce omaveloxolone dose to 50 mg once daily with close monitoring to detect adverse effects • If adverse effects emerge, coadministration with strong CYP3A4 inhibitor should be discontinued
Moderate CYP3A4 Inhibitor (such as, but not limited to: erythromycin, verapamil, diltiazem, cyclosporine)	Recommended to avoid concomitant use. If co-administration cannot be avoided: • Reduce omaveloxolone dose to 100 mg once daily with close monitoring to detect adverse effects • If adverse effects emerge, further reduce omaveloxolone dose to 50 mg once daily
Strong or Moderate CYP3A4 Inducer (such as, but not limited to: phenytoin, carbamazepine, rifampin)	Recommended to avoid concomitant use.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this for an FDA-approved indication for a patient 16 years of age and older?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Have baseline labs (ALT, AST, bilirubin, BNP and lipid parameters) been obtained prior to initiating therapy?	**Yes:** Document date and results here: _____ _____ _____ Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is baseline BNP > 200 pg/mL?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Has the provider documented the patient does not have severe hepatic impairment (Child-Pugh Class C)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. If patient has moderate liver impairment (Child-Pugh Class B) has the dose been modified to 100 mg once daily?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. If patient is taking other medications, are they CYP3A4 inhibitors or inducers that require omaveloxolone dosing adjustments as outlined in Table 1 and has the omaveloxolone dose been adjusted?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 6/23 (DM)
Implementation: TBD

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

OHSU Drug Effectiveness Review Project (DERP) Summary Report – CGRP Inhibitors

Date of Review: June 2023

Date of Last Review: October 2021
End Date of DERP Literature Search: November 2022

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

Plain Language Summary:

- This document is a summary of a research report from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). They studied a group of medicines called calcitonin gene-related peptide (CGRP) inhibitors approved in the United States to treat migraine headaches.
- A migraine headache is a moderate to severe throbbing pain that is usually on one side of the head. A migraine headache usually gets worse with light, physical activity, noises, or smells and often causes the affected person to have nausea or vomiting.
- CGRP inhibitor medicines are used to either prevent migraines or to treat a migraine as it happens. There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults: atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant. CGRP inhibitors come in different forms. Some are made to be long acting and given by injection into the skin or into the veins. Other forms may be shorter acting and taken by mouth. Some are used to treat a migraine headache, while others are used to prevent or decrease how often the headaches happen.
- The DERP found that at 12 weeks, most CGRP inhibitors (eptinezumab, erenumab, Fremanezumab, galcanezumab, and sometimes atogepant or rimegepant) helped reduce the number of migraines per month by about 2 days and improved the quality of life in people with regular migraines compared to no use of this medicine.
- DERP also found that certain CGRP inhibitors (eptinezumab, rimegepant, ubrogepant, and zavegepant) helped stop migraine pain and improved ability to do daily living tasks within 2 hours of taking the medicine.
- This report did not find that people taking CGRP inhibitor medicines had many harmful side-effects, but it is not clear how safe and helpful these medicines are if used often in a short time period or for longer than 12 to 16 weeks.
- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of CGRP inhibitor medicines.

Research Questions:

1. What is the new comparative evidence for efficacy and effectiveness for calcitonin gene-related peptide (CGRP) inhibitors for preventative and acute migraine treatment for the outcomes of headache frequency, reduction in the number of migraines, and freedom from pain?
2. What is the evidence for safety associated with CGRP inhibitors when used for the prevention of migraines and acute migraine treatment (e.g. withdrawals due to adverse events or severe adverse events)?

Author: Dave Engen, PharmD

3. Are there subpopulations in which CGRP inhibitors would be more effective or cause less harm in the treatment of acute migraines or migraine prevention?

Conclusions:

- The evidence included in this review is based on findings from the 2023 Drug Effectiveness Review Project (DERP) report on CGRP inhibitors.[1] Drugs included in the review are atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant (**Table 1**).[1] For migraine prevention, the magnitude of treatment effect of CGRP inhibitors was modest among all studies with approximately 0.4 to 3.7 days reduction compared to placebo.[1] Of the studies that evaluated headache severity with the 6-item headache impact test (HIT-6), 15 out of 17 trials reported reductions of 1.9 points or more (higher scores indicate greater impact on quality of life [QoL]; minimum clinically important difference [MCID] 1.5 points).[1]

*Chronic Migraine Prevention (**Table 2**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab and galcanezumab reduce the number of migraine days per month (decrease of 1.7 to 2.7 days a month) at 12 weeks compared to placebo. [1]
- QoL was improved, compared to placebo, with the use of eptinezumab, erenumab, and fremanezumab at 12 weeks as measured by the HIT-6 with a difference of 1.1 to 5.6 points, which suggests a variable clinical benefit (4 randomized controlled trials (RCTs); moderate quality of evidence); galcanezumab was more effective than placebo at improvements in QoL based on the Migraine-specific quality of life score (MSQL) measure (moderate quality of evidence). The clinical significance of QoL improvements based on the MSQL are unclear.[1]

*Episodic Migraine Prevention (**Table 3**)*

- The number of migraine days per month were reduced with atogepant, eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, with a difference ranging from -0.4 to -3.0 days (18 RCTs; moderate quality of evidence).[1]
- Erenumab, fremanezumab, and galcanezumab were more effective than placebo at improving quality of life based on moderate quality of evidence.[1]

*Chronic or Episodic Migraine [Mixed Populations of Both Types] (**Table 4**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant reduce the number of migraine days per month (range 0.8 to 3.7 fewer days per month) for chronic or episodic migraine at 12 to 24 weeks compared to placebo (5 RCTs).[1]
- There was a statistically significant decrease in migraine days per month for erenumab therapy compared to topiramate (decrease of 1.8 days, 95% confidence interval [CI], -1.3 to -2.4; moderate quality of evidence); erenumab treatment was also associated with larger QoL improvements (moderate quality of evidence).[1]
- There was moderate quality of evidence that eptinezumab and fremanezumab were more effective at improvement of functioning as measured by the HIT-6 (range of effects in mean difference 3.0 points to 5.4 points) compared to placebo which is suggestive of clinical benefit.[1]

*Acute Migraine Treatment **(Table 5**)*

- For the outcome of proportion of patients with freedom from pain at 2 hours, rimegepant and ubrogepant were more effective than placebo (difference range of 7.4% to 16.6%) based on moderate quality of evidence.[1]
- Zavegepant is the newest CGRP inhibitor agent recently FDA approved for acute migraine treatment.[1] One phase 3 RCT reported that at 2 hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (risk difference [RD] 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively) based on low quality evidence.[1] There was no significant difference in these outcomes for zavegepant 5 mg.[1]

Cluster Headache Prevention

- Compared to placebo, there was low quality evidence that galcanezumab was more effective in the short term (1 to 3 weeks) prevention of cluster headache (2.2 to 3.5 fewer attacks) but no difference in cluster headache prevention at weeks 8 to 12.[1]

Acute Cluster Headache Treatment

- No studies were identified with CGRP inhibitors used for acute cluster headache treatment.[1]

Adverse Effects from CGRP Inhibitors

- There was only low quality of evidence available for the comparison of adverse events (AEs) between CGRP inhibitors and placebo for all treatment studied.[1] Adverse events (e.g. constipation, injection site pain, infection), severe adverse events, and discontinuations due to adverse events were rare and similar to placebo for the majority of CGRP inhibitors. [1] Many of the included studies only evaluated treatment of one or few attacks, which may limit the capturing of harms data.

Subgroup Differences in Efficacy and Adverse Events

- There is insufficient evidence for the use of CGRP inhibitors in different subgroups or evidence of benefit beyond 24 weeks. [1]
- There is insufficient evidence of comparative differences between CGRP inhibitors or their use in combination with any other agent.

Recommendations:

- After clinical review no changes to the preferred drug list (PDL) are recommended.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- A review in October 2021 updated PA requirements for all therapies in the CGRP inhibitor PDL class. Current PA requires documentation of at least 4 migraines per month, failure of FDA approved migraine prophylactic therapies (beta-blockers, anticonvulsants, and tricyclic antidepressants) and a specialist consult for approval. Erenumab and fremanezumab are currently preferred therapy options in the CGRP inhibitor PDL class.
- There were fewer than 100 claims for CGRP inhibitors during first quarter of 2023 for Oregon Health Plan (OHP) Fee-for-Service (FFS) population.

Methods:

The January 2023 drug class report on Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

CGRP inhibitors are migraine therapies used to block CRGP, which is thought to play a role in migraine prevention, acute migraine treatment and cluster headache.[1] There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults (Table 1).[1] CGRP inhibitors come in various formulations and may be administered subcutaneously [SC], intravenously [IV], or orally.[1] Some agents are monoclonal antibodies that target the CGRP receptor (erenumab) or CGRP ligand (eptinezumab, fremanezumab, and galcanezumab), while others are small molecule agents that inhibit the CGRP receptor (atogepant, rimegepant, ubrogepant, and zavegepant).[1]

Table 1. CGRP Inhibitors Included in DERP Report[1]

Drug	Dose	Approval Date	Approved Indication	Number of RCTs Included
Atogepant QUILIPTA	10 mg, 30 mg, or 60 mg orally once daily	September 2021	Migraine Prevention	2
Eptinezumab VYEPTI	100 mg or 300 mg IV every 3 months	February 2020	Migraine Prevention	6
Erenumab AIMOVIG	70 mg or 140 mg SC every month	May 2018	Migraine Prevention	9
Fremanezumab AJOVY	225 mg SC monthly or 675 mg SC every 3 months	September 2018	Migraine Prevention	7
Galcanezumab EMGALITY	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Prevention	9
Rimegepant NURTEC	75 mg orally as needed for acute migraine attack	February 2020; May 2021 (new indication)	Acute Migraine Treatment Migraine Prevention	3
Ubrogepant UBRELVY	50 mg or 100 mg once orally for acute migraine attack, may repeat dose	December 2019	Acute Migraine Treatment	4
Zavegepant ZAVZPRET	10 mg (one spray) intranasally per 24 hours*	March 2023*	Acute Migraine Treatment	1

*=FDA labeling; product availability anticipated July 2023.

The purpose of this DERP report is to update evidence for the use of CGRP inhibitors since the previous published report in April 2020.[1] Literature was searched through November 8, 2022.[1] Main outcomes of interest were migraine or headache days per month or pain relief for acute migraine, functional outcomes, QoL, SAEs, and discontinuations due to AEs.[1] There is no established clinically important difference for headache day reduction in migraine prevention. Quality of life assessment tools used for the determination of headache severity were the HIT-6, MSQL and Migraine Disability Assessment (MIDAS).[1] The HIT-6 consists of 6 items (pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress) that are ranked from "never", "rarely", "sometime", "very often" or "always".[1,2] Higher HIT-6 scores are related to a greater impact on quality of life with a range of 36-78 points.[1,2] A score of 60 or more is considered severe impact on QoL.[2] A change of 1.5 units has been suggested as the MCID for the HIT-6 instrument based on clinically relevant changes in primary care populations with migraines.[1,2] The MSQL is a 14-item questionnaire used to determine migraine disability with scores ranging from 0-100, higher scores indicate a higher quality of life.[1,2] A 6-point scale is used to rate disability from "none of the time" to "all of the time", which are assigned a score of 1-6.[1,2] The MIDAS test is used to quantify headache disability based on a 7-item questionnaire.[1,2] The score is based on activity limitations ranging from little or no disability (0-5) to severe disability (21 or more).[1,2] For the MIDAS, as with many of the migraine quality of life assessments, the scores are not well defined and the MCID has not been determined. A total of 15 new RCTs were identified for a total trial inclusion of 42.[1] All trials were placebo-controlled and there was

insufficient evidence for direct comparison of different CGRP inhibitors.[1] One RCT compared rimegepant with sumatriptan for acute migraine treatment and 1 RCT compared erenumab with topiramate for the prevention of chronic or episodic migraine.[1] The quality of studies was considered moderate except for 1 poor quality trial.[1]

Chronic Migraine Prevention

Eptinezumab, erenumab, fremanezumab, and galcanezumab are used for the prevention of chronic migraine. Erenumab and galcanezumab were studied in one randomized controlled trial, eptinezumab in 2 trials, and fremanezumab in 3 trials.[1] Patients in the studies had a mean of 14.1 days to 19.6 days migraine days per month.[1] Outcomes with moderate evidence are presented in Table 2. All therapies were found to be more effective than placebo for the outcomes of number of migraine days per month, for the percent of patients with a 50% reduction in migraine days, and days with acute headache medication use per month.[1] Eptinezumab, erenumab, and fremanezumab were more effective at improving functioning at 12 weeks compared to placebo as measured by the HIT-6 (range 1.1 to 5.6 points).[1] The evidence for serious adverse events and discontinuations due to adverse events were associated with low or very low quality of evidence.[1] Trial summaries for the individual drugs and their outcome measures are presented below.

Table 2. CGRP Inhibitors for Chronic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Eptinezumab	*Dodick et al* 100 mg: -2.1 (-3.8 to -0.4) 300 mg: -2.7 (-4.4 to -0.9) *Lipton et al* 100 mg: -2.0 (-2.9 to -1.2) 300 mg: -2.6 (-3.4 to -1.7)	2 RCTs; Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg and 140-mg doses: -2.5 (-3.5 to -1.4)	1 RCT; Weeks 9 to 12	
Fremanezumab	*Bigal et al** 225 mg (monthly): -1.8 (-3.5 to -0.14) 900 mg (quarterly): -2.0 (-3.7 to -0.26) *Sakai et al* 225 mg (monthly): -1.7 (-2.5 to -0.8) 675 mg (quarterly): -1.7 (-2.6 to -0.8) *Silberstein et al* 225 mg (monthly): -1.8 (No CI reported) 675 mg (quarterly): -1.7 (No CI reported)	3 RCTs; Weeks 9 to 12 Monthly Quarterly Weeks 9 to 12	

Galcanezumab	Range: -2.1 to -1.9	1 RCT; Weeks 4 to 12	
	Outcome: Percentage of patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Dodick et al* 100 mg: 14.6%/NNT 7 (No CI reported) 300 mg: 16.5%/NNT 7 (No CI reported) *Lipton et al* 100 mg: 18.2% (11.1 to 25.4)/ NNT 6 300 mg: 22.1% (14.9 to 29.2)/ NNT 5	2 RCTs Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg: RR 1.70 (1.29 to 2.23) 140-mg: RR 1.75 (1.34 to 2.30)	1 RCT 12 weeks	
Fremanezumab	*Sakai et al* 225 mg (monthly): 15.9% (7.8 to 24.0)/NNT 7 675 mg (quarterly): 15.9% (7.9 to 24.0)/NNT 7 *Silberstein et al** 225 mg: RD 22.7% (16.4 to 29.1)/NNT 5 675 mg: 19.5% (13.3 to 25.8)/NNT 6	2 RCTs Weeks 4 to 16 Weeks 9 to 12	
Galcanezumab	120 mg: 28%/NNT 4 (No CI reported) 240 mg: 28%/NNT 4 (No CI reported)	1 RCT Weeks 4 to 12	
	Outcome: Days with acute migraine medication use per month		
Erenumab	70 mg: -1.9 (-2.6 to -1.1) 140 mg: -2.6 (95% CI, -3.3 to -1.8)	1 RCT Weeks 9 to 12	Moderate
Fremanezumab	*Bigal et al** 225 mg: -2.2 (-4.0 to 0.3) 900 mg: -2.0 (-3.9 to -0.20) *Silberstein et al** 225 mg: (monthly): -2.3 (No CI reported) 675 mg (quarterly): -1.8 (No CI reported) *Sakai et al* 225 mg (monthly): -1.3 (-2.2 to -0.4) 675 mg (quarterly): -1.4 (-2.3 to -0.6)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Weeks 4 to 16	Moderate

Galcanezumab	*Detke et al* 120 mg: -2.5 days (-3.3 to -1.8) 240 mg: -2.0 days (-2.8 to -1.3)	1 RCT Weeks 4 to 12	Moderate
	Outcome: Mean point change in HIT-6		
Eptinezumab	100 mg: -1.7 (No CI reported) 300 mg: -4.2 (-6.3 to -2.1) -2.9 (-3.9 to -1.8)	1 RCT Week 12	Moderate
Erenumab	70 mg: -5.6 (-6.5 to -4.6) 140 mg: -3.1 (-3.9 to -2.3)	1 RCT Week 12	
Fremanezumab	*Sakai et al* 225 mg (monthly): -1.6 (-2.9 to -0.2) 675 mg (quarterly): -1.5 (-2.9 to -0.2) *Silberstein et al** 225 mg: (monthly): -2.4 (No CI reported) 675 mg (quarterly): -1.9 (No CI reported)	2 RCTs Weeks 4 to 16 Week 12	
	Outcome: Mean point change in MSQL		
Galcanezumab	120 mg: -5.1 (-8.0 to -2.1) 240 mg: -6.3 (-9.6 to -3.0)	1 RCT Weeks 4 to 12	Moderate

*=Patients in the 225-mg group received 675-mg of fremanezumab at baseline and 225-mg of fremanezumab at weeks 4 and 8
Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Episodic Migraine Prevention Atogepant, eptinezumab, erenumab, fremanezumab, and galcanezumab were studied for episodic migraine prevention.[1] Patients had a history of 6.6 to 11.3 migraine headache days per month at baseline.[1] All therapies were more effective than placebo for the reduction in mean number of headache days per month by 1 to 2 days (range 0.4 days to 3 days).[1] All 5 drugs improved QoL/functional measures although there were different instruments employed (e.g. HIT-6, MIDAS, MSQL) and variable quality of evidence (moderate quality evidence for erenumab, fremanezumab, and galcanezumab; low quality evidence for atogepant and eptinezumab).[1] The evidence for serious adverse events and discontinuations due to adverse events were similar to placebo (very low quality of evidence).[1] Trial summaries for the individual drugs and their primary outcome measures with at least moderate quality evidence are presented in **Table 3**.

Table 3. CGRP Inhibitors for Episodic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Atogepant	*Ailani et al* 10-mg: -1.2 (-1.8 to -0.6) 30-mg: -1.4 (-1.9 to -0.8) 60-mg: -1.7 (-2.3 to -1.2) *Goadsby et al* 10-mg: -1.2 (-1.9 to -0.4) 30-mg: -0.9 (-1.6 to -0.3) 60-mg: -0.7 (-1.4 to -0.1)	2 RCTs Week 12 Week 12	Moderate
Eptinezumab	*Ashina et al.* 100-mg: -0.7 (-1.3 to -0.1) 300-mg: -1.1 (-1.7 to -0.5) *Dodick et al.* 1,000-mg: -1.0 (-2.0 to 0.1)	2 RCTs Week 12 Weeks 5 to 8	
Erenumab	*Dodick et al; Kawata et al.* 70-mg: -1.0 (-1.6 to -0.5) *Goadsby et al.; Buse et al.; Kawata et al.* 70-mg: -1.4 (-1.9 to -0.9) 140-mg: -1.9 (-2.3 to -1.4) *Sakai et al.* 70-mg: -2.3 (-3.0 to -1.6) 140-mg: -1.9 (-2.6 to -1.2) *Sun et al.* 70-mg: -1.1 (-2.1 to -0.2) *Wang et al.* 70-mg: -1.1 (-1.8 to -0.4) 140-mg: -1.7 (-2.5 to -0.9)	6 RCTs Weeks 9 to 12 Months 4 to 6 Months 4 to 6 Weeks 9 to 12 Week 12	
Fremanezumab	*Bigal et al.* 225-mg: -2.8 (-4.1 to -1.6)	3 RCTs Weeks 9 to 12	

	675-mg: -2.6 (-3.9 to -1.4) *Dodick et al.* 225-mg: -1.5 (-2.0 to -0.9) 675-mg: -1.3 (-1.8 to -0.7) *Sakai et al.* 225-mg: -3.0 (-3.7 to -2.2) 675-mg: -3.0 (-3.8 to -2.2)	 Weeks 9 to 12 Week 12	
Galcanezumab	*Dodick et al.* 1.2 (90% CI, -1.9 to -0.6) *Skljarevski et al.; Oakes et al.; Ayer et al.* 120-mg: -0.9 (No CI reported) 300-mg: -0.9 (No CI reported) *Skljarevski et al* 120 mg: -2.0 (-2.6 to -1.5) 240-mg: -1.9 (-2.4 to -1.4) *Stauffer et al.* 120-mg: -1.9 (-2.5 to -1.4) 240-mg: -1.8 (-2.3 to -1.2)	5 RCTs Weeks 9 to 12 Weeks 9 to 12 6 months 6 months	
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Ashina et al.* 100 mg: RD = 12.4 (3.2 to 21.5)/NNT 9 300 mg: 18.9 (9.8 to 28.0)/NNT 6	2 RCTs Week 12	Moderate
Erenumab	*Reuter et al.* 140-mg: OR, 2.7 (1.4 to 5.2) *Sakai et al.* 70 mg: OR = 5.6 (2.6 to 12.1) 140 mg: OR = 4.7 (2.2 to 10.0) *Goadsby et al.* 70 mg: OR = 2.1 (1.5 to 2.9) 140 mg: OR = 2.8 (2.0 to 3.9)	6 RCTs Weeks 9 to 12 Weeks 9 to 12 Months 4 to 6	

	Sun et al 70 mg: OR = 2.0 (1.2 to 3.4) *Wang et al.* 70 mg: OR = 1.5 (1.1 to 2.1) 140 mg: OR = 2.2 (1.6 to 3.2) *Dodick et al.* 70 mg: OR = 1.59 (1.12 to 2.27)	Weeks 9 to 12 Week 12 Weeks 9 to 12	
Fremanezumab	*Bigal et al.* 225 mg: RD = 21.2% (7.6 to 34.7)/NNT 5 675 mg: RD = 22.7% (9.2 to 36.1)/NNT 5 *Dodick et al.* 225 mg: RD = 19.8% (12.0 to 27.6)/NNT 6 675 mg: RD = 16.5% (8.9 to 24.1)/NNT 7 *Sakai et al* 225 mg monthly: RD = 30.1% (19.6 to 40.6)/NNT 4 675 mg quarterly: RD = 34.1% (23.4 to 44.7)/NNT 3	Weeks 9 to 12 Weeks 9 to 12 Months 4 to 6	
Galcanezumab	*Dodick et al.* 150 mg (every 2 weeks): RD = 25.2% (12.1 to 38.4)/NNT 4 *Sakai et al.; Shibita et al.* 120 mg: RD = 29.1% (18.6 to 39.7)/NNT 4 240 mg: RD = 27.8% (17.3 to 38.4)/NNT 4 *Skljarevski et al.* 120 mg: RD = 23.3% (15.6 to 31.0)/NNT 5 240 mg:	5 RCTs Weeks 9 to 12 Months 1 to 6 Weeks 9 to 12	

	RD = 20.5% (12.7 to 28.3)/NNT 5 *Stauffer et al.* 120 mg: RD = 23.8% (15.8 to 31.8)/NNT 5 240 mg: RD = 22.5% (14.4 to 30.6)/NNT 5	6 months	
	Outcome: Mean point change in HIT-6 from baseline		
Erenumab	*Dodick et al., Reuter et al., Sakai et al., Goadsby et al., Sun et al, Wang et al.* HIT-6 Improvement: Range = -3.0 to -1	6 RCTs Weeks 9 to 12	Moderate
	Outcome: Mean point change in MIDAS/MSQL from baseline		
Fremanezumab	*Bigal et al.* (MIDAS) 225 mg: -14.5 (-26.8 to -2.2) 675 mg: -15.2 (-27.6 to -2.8) *Dodick et al.* (MIDAS) 225 mg: -7.0 (-10.5 to -3.5) 675 mg: -5.4 (-8.9 to -1.9) *Sakai et al.* (MIDAS) 225 mg: -5.2 (-8.1 to -2.3) 675 mg: -5.1 (-8.1 to -2.2)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Week 12	Moderate
Galcanezumab	*Dodick et al., Sakai et al., Shibata et al., Tatsuoka et al., Skljarevski et al* MIDAS: Range = -9.2 to -3.0 MSQL: Range = -8.8 to -5.8	5 RCTs Months 4 to 6 Months 4 to 6	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MIDAS = Migraine Disability Assessment; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Chronic or Episodic Migraine Prevention

For chronic or episodic migraine prevention (study populations included both types and results were not stratified), there was moderate quality of evidence from 5 RCTs that eptinezumab, erenumab, fremanezumab, galcanezumab, and rimegepant were more effective than placebo in reduction of migraine days per month (range 0.8 to 3.7 fewer days per month).[1] Only eptinezumab, erenumab, and fremanezumab were more effective than placebo in outcomes of percentage of participants with at least 50% reduction in migraine days (moderate quality evidence).[1] There was moderate quality evidence that erenumab

resulted in a statistically significant decrease in migraine days per month compared with topiramate (MD -1.8 [95% CI, -1.3 to -2.4]; it also was associated with larger improvements in QoL (moderate CoE). About 39% of the topiramate group had at least 1 adverse event leading to treatment discontinuation compared to 11% of those on erenumab which may have resulted in significant attrition bias. Eptinezumab and fremanezumab were more effective than placebo at improvement in function as measured by the HIT-6 (range 3.0 to 5.4 points; moderate quality of evidence).[1] **Table 4** summarizes these findings.

Table 4. CGRP Inhibitors for Chronic or Episodic Migraine Prevention (Mixed Populations)[1]

Drug	**Results** (Mean difference from placebo unless noted; 95% CI; all reported statistically significant results based on an alpha equal to .05)	**Number of Trials; Assessment Timing**	**Quality of Evidence**
	Outcome: Migraine days per month		
Eptinezumab	100-mg: -2.7 (-3.4 to -2.0) 300-mg: -3.2 (-3.9 to -2.5)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg or 140 mg: -1.6 (-2.5 to -0.7)	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly): -3.5 (-4.2 to -2.8) 675 mg (quarterly): -3.1 (-3.8 to -2.4)	1 RCT Weeks 1 to 12	Moderate
Galcanezumab	120 mg: -3.1 (-3.9 to -2.3)	1 RCT Weeks 4 to 16	Moderate
Rimegepant	75 mg: -0.8 (-1.5 to -0.2)	1 RCT Weeks 9 to 12	Moderate
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	100 mg: 29.1%/NNT 4 300 mg: 36.4%/NNT 3	1 RCT Weeks 1 to 12	Moderate
Erenumab	*Reuter et al* (vs Topiramate) Erenumab: 55% Topiramate: 31% RD = 22%/NNT 5	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly) and 675 mg (quarterly): 34%/NNT	1 RCT Weeks 1 to 12	Moderate
	Outcome: Mean Change HIT-6 Score		
Eptinezumab	100 mg: -3.8 (-5.0 to -2.5) 300 mg: -5.4 (-6.7 to -4.2)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg and 140 mg (vs Topiramate): -3.2 (-4.3 to -2.1)	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg: -3.8 (-5.0 to -2.7) 675 mg: -3.0 (-4.1 to -1.8)	1 RCT Week 12	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; NNT = number needed to treat; RCT = randomized controlled trial

Acute Migraine Treatment

Rimegepant and ubrogepant are two small molecule CGRP inhibitors used for the acute treatment of migraine. A third and the newest CGRP agent, zavegepant, had not yet been FDA approved at the time of the review.[1] Rimegepant and ubrogepant were studied in 3 randomized controlled trials (**Table 5**).[1] There was moderate quality evidence that rimegepant and ubrogepant were more effective than placebo for the outcomes of freedom from pain at 2 hours and freedom from most bothersome symptom at 2 hours.[1]

Zavegepant (Zavzpret®) was approved by the FDA in March 2023 after completion of the DERP report.[1] The efficacy and safety of zavegepant was studied in one phase 2/3, double blind RCT (N=1,581) at multiple sites in the US. The study included mostly females (86%) with a 1-year history of migraine of at least 2 attacks per month where untreated migraines lasted 4 to 72 hours.[1] Patients with history of hemiplegic migraine, unstable medical conditions, opioid use, or recent use of nasal sprays were excluded.[1] Patients were randomized into 4 groups of roughly equal proportions and given either zavegepant 5-mg, 10-mg, 20-mg or placebo.[1] Primary endpoints were freedom from pain or freedom from most bothersome symptoms at 2 hours post-dose.[1] There was low quality evidence that at two hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (RD 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively).[1] Zavegepant 5 mg comparison to placebo did not reach statistical significance for the pre-defined study outcomes.[1]

The new CGRP inhibitor agent zavegepant and those agents with at least moderate quality evidence for acute migraine treatment outcomes are reported in Table 5.

Table 5. CGRP Inhibitors for Acute Migraine Treatment[1]

Drug	**Results*** (Mean difference from placebo unless noted) **Outcome:** Proportion patients with freedom from pain at 2 hours post-dose	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Rimegepant	vs. Placebo *Croop et al* 75 mg: 10.4% (6.5% to 14.2%) /NNT 10 *Lipton et al* 7.6% (3.3% to 11.9%)/NNT 14 *Marcus et al* 16.2% (5.2% to 27.1%)/NNT 7 vs. Sumatriptan *Marcus et al* -3.6% (-17.2% to 9.9%) *No statistically significant difference as calculated by DERP authors*	3 RCTs; 2 hours all trials 1 RCT N/A	Moderate
Ubrogepant	*Dodick et al* 50-mg: 7.4% (2.6% to 12.1%)/NNT 14 100-mg: 9.4% (4.6% to 14.2%)/NNT 11	3 RCTs; 2 hours all trials	Moderate

	Lipton et al 50-mg: 7.5% (2.6 % to 12.5%)/NNT 14 *Voss et al* 50-mg: 12.0% (2.6 to 21.4)/NNT 9 100-mg: 16.6% (12.4 to 22.4)/NNT 6		
Zavegepant	*Croop et al* 5 mg: 4.2% (not statistically significant) 10 mg: 7% (1.6 to 12.5)/NNT 15 20 mg: 7.7% (2.2 to 13.1)/NNT 13	1 RCT; 2 hours	Low
	Outcome: Proportion of patients with freedom from most bothersome symptom at 2 hours post-dose		
Rimegepant	*Croop et al* 75 mg: 8.3% (3.4% to 13.2%)/NNT 13 *Lipton et al* 12.4% (6.9% to 17.9%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Ubrogepant	*Dodick et al* 50-mg: 10.8% (4.6% to 17.0%)/NNT 10 100-mg: 10.0% (3.9% to 16.1%)/NNT 10 *Lipton et al* 50-mg: 11.5% (5.4% to 17.5%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Zavegepant	*Croop et al* 5 mg: 5.4% (not statistically significant) 10 mg: 8.3% (1.5 to 15.0)/NNT 13 20 mg: 8.9% (2.2 to 15.6)/ NNT 12	1 RCT; 2 hours	Low

*=95% CI; all reported statistically significant results based on an alpha equal to .05 unless otherwise noted
Abbreviations: CI = confidence interval; NNT = number needed to treat; RCT = randomized controlled trial

Acute Cluster Headache Treatment
There were no new studies identified that assessed the effectiveness of CGRP inhibitors for acute cluster headache prevention since the previous DERP report.[1]

Cluster Headache Prevention
For cluster headache prevention, there was low-quality evidence that galcanezumab is not effective and very low quality of evidence for harms due to the rarity of events.[1] Although galcanezumab resulted in statistically significant reduction in cluster headache attack frequency per week during weeks 1 through 3 compared to placebo (range 2.2 to 3.5 fewer), there was no difference at weeks 8 to 12 (range 0.8 fewer to 1.3 more attacks per week).[1]

Adverse Events from CGRP Inhibitors

The DERP review was unable to determine a relationship between active CGRP treatment and adverse events (e.g. constipation, injection site pain, infection, etc.) due to the infrequent reporting of severe adverse events and discontinuations due to adverse events.[1] The frequency of AEs, SAEs, and discontinuations due to AEs was similar between active treatment groups and placebo for virtually all indications, drugs, and dosages (very low quality of evidence).[1] Erenumab had fewer discontinuations due to AEs compared to topiramate (moderate quality of evidence).[1] No discontinuations due to AEs were reported in trials that compared rimegepant to sumatriptan (very low quality of evidence).[1] Liver injury due to treatment was uncommon with CGRP treatment in studies that reported that outcome.[1]

Subgroup Differences in Efficacy and Adverse Events

There were few studies that reported subgroup findings.[1] Five fremanezumab studies evaluated efficacy among participants who were not taking preventative medications compared to the full study population and reported similar efficacy.[1] There were no studies found for use of CGRP inhibitors in combination with any other agent.

Evidence Limitations

Studies were industry sponsored and evidence was downgraded due manufacturer sponsorship and extensive involvement in the trials themselves.[1] There were no head-to-head trials that directly compared two or more CGRP inhibitors.[1] Many trials were of short duration (12 weeks) preventing long-term evidence for efficacy and harms in a condition that is typically treated chronically as long-term therapy.[1] Only studies of single, acute migraine attacks were assessed, therefore effectiveness and safety of repeated use is unknown.[1] Most studies employed an electronic headache diary during a run-in phase so generalizability to a less selective population was uncertain.[1] Patients who were pregnant or those with clinically significant psychiatric or medical conditions were excluded so the effects in a less selective study population was unknown.[1] Most studies included a high majority of females and did not report information on race and ethnicity.[1]

References:

1. Drug Effectiveness and Review Project (DERP). Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention. Center for Evidence-based Policy, Oregon Health & Science University; 2023.
2. Institute for Clinical and Economic Review. Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final Evidence Report. July 2018. Accessed March 14, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_Migraine_Final_Evidence_Report_070318.pdf

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
erenumab-aooe	AIMOVIG AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY SYRINGE	SYRINGE	SQ	Y
atogepant	QULIPTA	TABLET	PO	N
eptinezumab-jjmr	VYEPTI	VIAL	IV	N
galcanezumab-gnlm	EMGALITY PEN	PEN INJCTR	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
rimegepant sulfate	NURTEC ODT	TAB RAPDIS	PO	N
ubrogepant	UBRELVY	TABLET	PO	N
zavegepant	ZAVZPRET	SPRAY	NS	N

Appendix 2: Prior Authorization Criteria

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):

- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 6 months

Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonist pharmacy and practitioner 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. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
Atogepant	Preventative episodic migraine treatment
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment and preventative treatment of episodic migraine
Ubrogepant	Acute migraine treatment
Zavegepant	Acute migraine treatment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 6
6. Is the request for acute (abortive) migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #7
7. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	**Yes:** Go to #15	**No:** Go to #8

Approval Criteria		
8. Is the request for prophylactic therapy and there is documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	**Yes:** Document migraine days per month _____ Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different classes)? • Propranolol immediate-release, metoprolol, or atenolol • Topiramate, valproic acid, or divalproex sodium • Amitriptyline, nortriptyline, or venlafaxine OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the above migraine prophylaxis agents?	**Yes:** Document agents used and dates _____ _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
10. Is the request for erenumab and the patient has pre-existing hypertension or risk factors for hypertension?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 3 months
12. In a patient with acute migraines, has the patient failed to receive benefit from adequate trials of abortive therapy (2 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
13. Does the patient have chronic migraines?	**Yes**: Go to #14	**No**: Approve for 3 months

Approval Criteria		
14. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?	**Yes:** Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the patient failed to receive benefit from at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, prednisone, suboccipital steroid injection, topiramate)?	**Yes**: Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Is the renewal request for acute migraine treatment?	**Yes:** Go to #5	**No:** Go to #3
3. Is the renewal request for migraine prevention?	**Yes:** Go to #4	**No:** Go to # 6
4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response. Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical Appropriateness

7. Does the patient have documentation of a positive response, indicated by a reduction in the number of cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 6/23 (DE); 10/21 (KS), 8/20 (KS); 5/19; 9/18 (DE)
Implementation: TBD; 1/1/2022; 11/1/2018

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Prior Authorization Criteria Update:
Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis AND Targeted Immune Modulators for Autoimmune Conditions

Plain Language Summary:

- The Oregon Health Evidence Review Commission serves Oregon citizens by ensuring that certain medical procedures, devices and tests paid for with Medicaid health care dollars are safe and proven to work.[1] This Commission decides which health care services to put on the Oregon Health Plan's Prioritized List of Health Services.
- As of February 1, 2023 the Health Evidence Review Commission revised guidance regarding coverage for severe inflammatory skin disease medical treatments to require a 4-week trial and failure (or documented contraindication) of 2 topical medications or one oral medication that are proven to alleviate symptoms of atopic dermatitis (also known as eczema) before advancing to disease modifying drug such as dupilumab or upadacitinib.
- The Drug Use Research & Management program is recommending the atopic dermatitis prior authorization criteria be revised to align with the guidance approved by the Health Evidence Review Commission.

Purpose of Update: Revise prior authorization (PA) criteria for targeted immune modulators (TIMs) used to treat atopic dermatitis (i.e., dupilumab and upadacitinib) to align with updated 2023 Health Evidence Review Commission (HERC) guidance.

The HERC revised Guideline Note 21 which provides funding guidance for severe inflammatory skin diseases effective February 1, 2023. For severe atopic dermatitis/eczema, funded treatments include: topical moderate- to high- potency corticosteroids, topical calcineurin inhibitors (i.e. tacrolimus), and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, or oral corticosteroids).[1] Targeted immune modulators (i.e. dupilumab and upadacitinib) are included on this line when:

A) Prescribed in consultation with a dermatologist or allergist or immunologist, AND

B) The patient has failed (defined as inadequate efficacy, intolerable side effects, or side effects that pose a health risk) either:

   1) a 4-week trial of a combination of a topical moderate to high potency topical steroid and a topical non-steroidal agent (e.g., tacrolimus)

   OR

   2) an oral immunomodulator.[1]

Recommendation:

- Revise PA criteria for "Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis" and "Targeted Immune Modulators for Autoimmune Conditions" to require a 4-week trial and failure (or contraindication) of either moderate to high potency topical steroids in combination with a topical calcineurin inhibitor (e.g., tacrolimus) or an oral immunomodulator (e.g., cyclosporine, methotrexate, or oral corticosteroids) before approval of dupilumab or upadacitinib treatment for atopic dermatitis as presented in **Appendix 1**.

References:

1. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx. Accessed May 2, 2023.

Appendix 1. Proposed Prior Authorization Edits

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Promote use that is consistent with national clinical practice guidelines, medical evidence, and OHP-funded conditions. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators with indications for severe asthma, atopic dermatitis, or other indications (see **Table 2** below) for both pharmacy and physician-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

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. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	Maximum Dose
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID

Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma*	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Eosinophilic Esophagitis	Atopic Dermatitis (AD)	Other
Abrocitinib CIBINQO						≥12 yrs	
Benralizumab FASENRA	≥12 yrs						
Dupilumab DUPIXENT	≥6 yrs (or with oral corticosteroid dependent asthma)			≥18 yrs	≥12 yrs & weighing ≥40 kg	≥6 months	PN ≥18 yrs
Mepolizumab NUCALA	≥6 yrs			≥18 yrs			HES ≥ 12 yrs EPGA ≥18 yrs
Omalizumab XOLAIR		≥6 yrs		≥18 yrs			CSU ≥ 12 yrs
Reslizumab CINQAIR	≥18 yrs						
Tezepelumab TEZSPIRE			≥ 12 yrs				

Tralokinumab ADBRY						≥18 yrs	
*Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long-acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).							
Abbreviations: CSU = Chronic spontaneous urticaria; EPGA = Eosinophilic Granulomatosis with Polyangiitis; HES = Hyper-eosinophilic Syndrome; PN = prurigo nodularis							

Table 3. Abrocitinib Dosing Adjustments for Atopic Dermatitis

Assessment	Recommended Dose
CYP2C19 Poor Metabolizer	50 mg once daily and may increase to 100 mg once daily after 12 weeks if inadequate response to 50 mg once daily
GFR 30 to 59 mL/min	Start with 50 mg once daily and may increase to 100 mg once daily after 12 weeks if inadequate response to 50 mg once daily
GFR < 30 mL/min	Use is not recommended
Severe hepatic impairment (Child-Pugh Class C)	Use is not recommended

Table 4. FDA-Approved Dosing for Monoclonal Antibodies Used to Treat Severe Asthma Phenotypes

Generic Name	Brand Name	Asthma Indication	Initial Dose and Administration Route	Maintenance Dose and Administration Route
Benralizumab	FASENRA	Severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks for the first 3 doses	30 mg SC every 8 weeks
Dupilumab	DUPIXENT	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Ages 6 to 11 yo**:** An initial loading dose is not necessary Ages ≥ 12 yo : 400 mg to 600 mg SC x 1 dose	Ages 6 – 11 yo (weight 15 to 30 kg) 100 mg SC every 2 weeks OR 300 mg SC every 4 weeks Ages ≥ 12 yo: 200 to 300 mg SC every 2 weeks
Mepolizumab	NUCALA	Severe asthma with an eosinophilic phenotype	N/A	Ages ≥ 6 – 11 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks
Omalizumab	XOLAIR	Moderate to severe persistent asthma and positive allergy testing	N/A	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels
Reslizumab	CINQAIR	Severe asthma with an eosinophilic phenotype	N/A	3 mg/kg IV infusion every 4 weeks
Tezepelumab	TEZSPIRE	Severe asthma	N/A	210 mg SC every 4 weeks
Abbreviations: IgE = immunoglobulin E; IV = intravenous; kg = kilogram; mg = milligram; N/A = Not Applicable; SC = subcutaneous; yo = years old				

Table 5. Dupilumab Dosing by Indication

Indication	Dose (Subcutaneous)

Atopic Dermatitis in adults	600 mg followed by 300 mg every 2 weeks
Atopic Dermatitis in pediatric patients (aged 6 to 17 years)	600 mg followed by 300 mg every 4 weeks (15 to 29 kg) 400 mg followed by 200 mg every 2 weeks (30 to 59 kg) 600 mg followed by 300 mg every 2 weeks (≥ 60 kg)
Asthma in adults and adolescents (aged 12 years and older)	400 mg followed by 200 mg every 2 weeks or 600 mg followed by 300 mg every 2 weeks
Asthma in pediatric patients (aged 6 to 11 years)	100 mg every 2 weeks or 300 mg every 4 weeks (15 to 29 kg) 200 mg every 2 weeks (≥ 30 kg)
Chronic rhinosinusitis with nasal polyps in adults	300 mg every other week
Eosinophilic esophagitis in adults and adolescents (aged 12 years and older)	300 mg once a week
Prurigo nodularis in adults	600 mg followed by 300 mg given every 2 weeks

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication and indications (**Table 2**)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes**: Go to #4	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. Current Age < 21 years: Go to #4
4. Is the request for dupilumab?	**Yes:** Go to # 5	**No:** Go to #6
5. If the request is for dupilumab, is the dose appropriate for the indication (**Table 5**)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7

Approval Criteria		
7. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the diagnosis Severe Atopic Dermatitis (AD)? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following: o At least 10% body surface area involved, or o Hand, foot, face, or mucous membrane involvement	**Yes:** Go to #9	**No:** Go to #17
9. Is the medication being prescribed by or in consultation with a dermatologist, allergist, or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for abrocitinib?	**Yes:** Go to #11	**No:** Go to #16
11. Are baseline labs (platelets, lymphocytes, lipids) documented? *Note: Abrocitinib therapy should not be initiated if platelet count is < 150,000/mm^3, absolute lymphocyte count is < 500/mm^3, absolute neutrophil count is < 1,000/mm^3, or hemoglobin is < 8 g/dL	**Yes:** Go to #12 Document Lab and Date Obtained: Platelets:_____ Lymphocytes:_____ Lipids:_____ Hemoglobin:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Is the patient currently taking other targeted immune modulators or oral immunosuppressants?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. If the patient has renal or hepatic impairment has the dose been adjusted as described in Table 3?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the patient taking a strong CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2C9 inducer, CYP2C19 inducer, or antiplatelet inhibitor?	**Yes:** Go to #15	**No:** Go to #16
15. If the patient is taking a strong CYP2C19 inhibitor (e.g., fluvoxamine, fluoxetine), or CYP2C9 inhibitor (e.g., fluconazole, amiodarone), or CYP2C9 inducer (e.g., rifampin, phenobarbital), or CYP2C19 inducer (carbamazepine), or antiplatelet agent has the abrocitinib dose been adjusted in Table 3 or has the interacting drug been discontinued if necessary? *Note: agents with antiplatelet properties (NSAIDs, SSRIs, etc.) should not be used during the first 3 months of abrocitinib therapy. Do not use aspirin at doses ≥ 81 mg/day with abrocitinib during the first 3 months of therapy.	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
16. Does the patient have a documented contraindication or failed 4-week trial of either one the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) in combination with a topical calcineurin inhibitor (e.g., tacrolimus) ~~pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND~~OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, ~~azathioprine, mycophenolate mofetil,~~or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
17. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #18
18. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #19
19. Is the request for treatment of nasal polyps?	**Yes:** Go to #20	**No:** Go to #22
20. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to #21	**No:** Pass to RPh. Deny; medical appropriateness
21. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
22. Is the request for treatment of severe asthma?	**Yes:** Go to #23	**No:** Go to #30
23. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #24	**No:** Pass to RPh. Deny; medical appropriateness
24. Has the patient experienced one of the following: • at least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #25 Document number asthma exacerbations over the previous 12 months or oral corticosteroid dose over the previous 6 months or number of hospitalizations or ED visits in the past 12 months _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
25. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #26	**No:** Pass to RPh. Deny; medical appropriateness.
26. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #27
27. Is the request for tezepelumab?	**Yes:** Approve for up to 12 months.	No: Go to #28

Approval Criteria		
28. Is the request for omalizumab and can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #29
29. Is the request for asthma with an eosinophilic phenotype and can the prescriber provide documentation of one of the following biomarkers: • severe eosinophilic asthma, confirmed by blood eosinophil count ≥150 cells/μL OR • fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months?	**Yes:** Approve up to 12 months, based on dosing outlined in **Table 4**. Document eosinophil count (or FeNO date):_____	**No:** Pass to RPh. Deny; medical appropriateness.
30. Is the request for treatment of eosinophilic esophagitis?	**Yes:** Go to #31	**No:** Go to #32
31. Does the patient have a documented contraindication or failed trial of the following treatments: • Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone multi-use inhaler for at least 8 weeks (use nasal inhaler and swallow contents of the spray).	**Yes**: Document drug and dates trialed and intolerances (if applicable): _____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
32. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #33	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
33. Is there documentation from the provider that alternative treatments for the condition are inappropriate, unavailable, or ineffective?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with targeted immune modulator therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for asthma?	**Yes:** Go to #4	**No:** Go to #6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the number of emergency department (ED) visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request to renew therapy for another FDA approved indication?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports.* http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed May 2, 2023..
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.
3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

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P&T Review: *6/23 (DM); 10/22 (DM) 6/22 (DM); 8/21 (DM); 10/20 (KS),7/19; 7/18; 7/16*
Implementation: *TBD; 1/1/23; 7/1/22; 1/1/22; 9/1/21; 8/19/19, 8/15/18, 8/16*

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use of targeted immune modulators to OHP-funded diagnoses in adults. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both 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. Approved and Funded Indications for Targeted Immune Modulators

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo			aGVHD ≥ 2 yo
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥5 yo (Humira) ≥18 yo (biosimilars)		Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo			COVID ≥ 18 yo (hospitalized) NOMID DIRA
Apremilast (OTEZLA)				≥18 yo	≥18 yo				Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo			COVID ≥ 18 yo (hospitalized)
Brodalumab (SILIQ)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo Stills Disease ≥ 2 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo			Nr-axSpA ≥18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel & biosimilars)	≥18 yo	≥18 yo			
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥2 yo	≥18 yo	≥18 yo (Simponi)		
Guselkumab (TREMFYA)				≥18 yo	≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo				Nr-axSpA ≥18 yo
Risankizumab-rzaa (SKYRIZI)		≥18 yo		≥18 yo	≥ 18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo			CLL ≥18 yo DLBCL≥6 mo BL≥6 mo BLL≥6 mo B-AL≥6 mo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Atopic Dermatitis	Other
Sarilumab (KEVZARA)						≥18 yo			PMR ≥18 yo
Secukinumab (COSENTYX)	≥18 yo			≥6 yo	≥2 yo				ERA ≥ 4 yo Nr-axSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo					
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo			COVID ≥ 18 yo (hospitalized) CRS ≥2 yo GCA ≥18 yo SSc-ILD ≥ 18 yo
Tofacitinib (XELJANZ)	≥18 yo		≥2 yo active poly-articular course		≥18 yo	≥18 yo	≥18 yo		
Upadacitinib (RINVOQ)	≥18 yo				≥18 yo	≥18 yo	≥18 yo	≥12 yo	Nr-axSpA ≥18 yo
Ustekinumab (STELARA)		≥ 18 yo		≥6 yo	≥6 yo		≥18 yo		
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: aGVHD = acute Graft Versus Host Disease; BD = Behcet's Disease; BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; ERA = Enthesitis-Related Arthritis; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; Nr-axSpA = Non-Radiographic Axial Spondyloarthritis; PMR = Polymyalgia Rheumatica; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria	
1. What diagnosis is being treated?	Record ICD-10 code.

Approval Criteria		
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis, plaque psoriasis, and atopic dermatitis are unfunded, severe forms are funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded. C. Alopecia areata is unfunded. Psoriasis and atopic dermatitis are severe in nature when resulting in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's DLQI ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. For current age < 21 years: Go to #3.
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Deny, medical necessity.

Approval Criteria		
4. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment? * *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
5. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to # 6
6. Is the request for a non-preferred product and 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 Committee.	**Yes:** Inform prescriber of preferred alternatives. Go to #6	**No:** Go to # 7
7. Is the request for an FDA-approved medication with a corresponding diagnosis listed in the "Other" column of Table 1?	**Yes:** Approve for length of treatment or up to 1 year, whichever is longer.	**No:** Go to # 8
8. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 9	**No:** Go to # 10
9. Is this a request for a preferred agent OR if the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® branded product or an Enbrel® branded product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to # 11	**No**: Go to #12
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); AND • At least one other topical agent: calcipotriene, tazarotene, anthralin; AND • Phototherapy; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; AND • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for a drug FDA-approved for atopic dermatitis as defined in Table 1?	**Yes:** Go to # 13	**No**: Go to #14
13. Does the patient have a documented contraindication or failed a 4-week trial of either of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide), in combination with a topical calcineurin inhibitor (e.g., tacrolimus) ~~pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole), AND~~ OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, ~~azathioprine, mycophenolate mofetil,~~ or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
14. Is the diagnosis rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 15	**No:** Go to # 18
15. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; OR • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® branded product or an Enbrel® branded product for at least 3 months? AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to # 16 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
16. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to # 17	**No:** Approve for up to 6 months
17. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis

Approval Criteria		
18. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 19	**No:** Go to # 20
19. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90-day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198.	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
20. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 21	**No:** Go to # 25
21. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.
22. Is the request for risankizumab?	**Yes:** Go to #23	**No:** Go to # 24
23. Have baseline liver enzymes and bilirubin been obtained?	**Yes:** Go to #24 Document Labs & Date: LFTs:_____ Bilirubin:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
24. Is the request for a preferred product or has the patient tried and failed a 3-month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
25. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis, plaque psoriasis, ulcerative colitis, Crohn's disease, or rheumatoid arthritis?	**Yes:** Go to # 6	**No:** Go to # 2
2. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #3	**No:** Go to #4
3. Have the patient's symptoms improved with upadacitinib therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started, OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 5	**No:** Go to # 6
5. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/23 (DM); 10/22 (DM); 6/22(DM); 10/21; 10/20; 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*

Implementation: *TBD; 1/1/23; 7/1/22; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 12/12*

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Drug Class Update: Botulinum Toxins

Date of Review: June 2023

Date of Last Review: May 2014 (Botulinum Toxins)
May 2019 (Migraine)
Dates of Literature Search: 03/01/2018 - 02/23/2023

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

Purpose for Class Update:
The purpose of this review is to evaluate the literature for new high-quality evidence for the use of botulinum toxins (BoNT) and provide an approval route for unfunded conditions that will be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program. The Early and Periodic Screening, Diagnostic and Treatment program may allow for treatment of some conditions, for people under 21 years old who are enrolled in Medicaid, which are not normally covered under the Oregon Health Plan (OHP) fee-for-service (FFS) program.

Plain Language Summary:
- The review looks for new evidence for the use of botulinum toxins for medical conditions with a particular interest in evidence for use in adolescents and children under 21 years of age.
- Botulinum toxin is used for many different reasons; however, the Oregon Health Plan only covers those disease states that use botulinum toxin for medical purposes, such as migraine headaches or leaky bladder rather than cosmetic reasons such as minimizing wrinkles. Table 1 has a list of Food and Drug Administration (FDA) approved botulinum toxin products and the conditions that are approved to treat.
- Botulinum toxin is available as two types; botulinum toxin type A and botulinum toxin type B. One of the ways these types of botulinum toxins differ is by the different conditions that they have shown that they can effectively treat.

<u>Conditions that botulinum toxins were shown to be effective:</u>
- The Agency for Health Care Quality and Research reviewed the use of botulinum toxin A for the use in urinary incontinence (leaky bladder) and found that it was more effective than no treatment at curing the condition. Another review evaluated the use of botulinum toxin A in people with an increased urge to urinate and found that it was more helpful than placebo (sugar pill) in reducing these symptoms. The National Institute for Health and Care Excellence recommends the use of botulinum toxin A for adult women with leaky bladder (urinary incontinence) who have tried to take medications by mouth to decrease the number of leaks but still have symptoms.
- A review done by Cochrane Database of Systematic Reviews found that botulinum toxin B may be helpful to reduce excessive drooling in people that have a disease that affects nerve cells in the brain and spinal cord, by slightly reducing the amount of saliva production. A type of botulinum toxin, called incobotulinum toxin A, was studied by the Canadian Agency for Drugs and Technology in Health for the use in the treatment of excessive drooling when

caused by a disorder of the nervous system. Incobotulinum toxin A was found to be better than placebo (salt water injection) to decrease drooling based on one study.

- The use of botulinum toxin A was studied for the treatment of muscle spasms in the legs of children that have cerebral palsy and was found to help more than placebo in improving the child's ability to walk.
- A report by Cochrane Systematic Reviews found that for people that have unwanted muscle movements in their head and neck, may be helped with the use of botulinum toxin more than placebo. A similar review found that botulinum toxin A may be slightly more helpful at decreasing symptoms of this condition compared to another type of medication called an anticholinergic that is also used to treat this condition.
- In people who have unwanted eyelid closure, a review done by Cochrane Systematic Reviews found that botulinum toxin is slightly more effective than placebo in reducing the severity of this condition.
- Botulinum toxin was studied for people that have chronic migraine headaches, which is 15 or more migraine headaches a month. The review found that the use of botulinum toxin decreased the number of headaches each month by about two, compared to placebo.
- A review and recommendation made by the National Institute for Health and Care Excellence recommends that botulinum toxin may be an option in people that have multiple sclerosis, who have muscle spasms, if the recommendation is made by a specialist and they have tried other medications such as baclofen and gabapentin.
- A new drug, daxibotulinum toxin A (DAXIFY), was approved for decreasing wrinkles. There are no studies to determine if it is better or worse than existing treatments.

<u>Conditions treated with botulinum toxins that were not effective:</u>

- Botulinum toxin was studied in children who walk on their toes for no known reason. There was only one study included in this review that found a small decrease in the amount of toe walking with the use of botulinum toxin A but recommended more studies to determine if there was a true benefit.
- A review done by the Canadian Agency for Drugs and Technologies in Health reviewed the use of botulinum toxin A to help reduce pelvic pain in women and did not find good information to support using it for this purpose.
- The Drug Use Research and Management Group recommends that no changes be made to the current policy that is in place for the use of botulinum toxin in patients that have fee-for-service medical coverage. Members that are under 21 years of age and have need for botulinum toxin for the use of decreasing excessive drooling, caused by another medical condition, should be evaluated on a case-by-case basis to see if botulinum toxin may be helpful.

Research Questions:

1. Is there new comparative evidence evaluating treatments or preventative therapies using BoNT based on relevant disease states/conditions?
2. Is there new comparative harms data for BoNT treatments (e.g., withdrawals due to adverse events, severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain BoNT treatments are more effective or cause less harm?

Conclusions:

- There were 11 new systematic reviews and meta-analyses, two new guidelines, seven randomized controlled trials, and one new drug covering nine different types of disease states reviewed in this drug class update. There were no studies which specifically studied Medicaid patients.

Conditions in which literature supports the use of BoNT:

- A review by the Agency for Health Care Research and Quality (AHRQ) evaluated the use of botulinum neurotoxin type A (BoNT-A) for the use in urinary incontinence (UI) in women.[1] There was high-quality evidence that BoNT-A, compared to no treatment, demonstrated higher cure rates for urgency UI (odds ratio [OR] 4.9; 95% confidence interval [CI], 2.82 to 8.65).[1] There was high-quality evidence that in all types of UI BoNT-A was more effective than no treatment for cure rates (OR 5.67; 95 CI, 2.80 to 11.4).[1]
- There is high-quality evidence from a 2018 Canadian Agency for Drugs and Technologies in Health (CADTH) review that BoNT-A improves urgency symptoms, more than placebo, in people with overactive bladder (OAB).[2] There is low-quality evidence that BoNT-A reduces pain symptoms in people with bladder pain syndrome (BPS)/interstitial cystitis (IC).[2]
- A Cochrane Review found moderate-quality evidence of a small benefit, when compared to placebo, for the treatment of sialorrhea in adults with motor neuron disease (MND).[3] A reduction of 0.5 mL in saliva production in 5 minutes was demonstrated with botulinum neurotoxin type B (BoNT-B) compared to placebo at 8 weeks. The clinical significance of this is unknown. There was no evidence to support the use of BoNT-A for the treatment of sialorrhea.
- A review done by Cochrane evaluated BoNT-A use in children with cerebral palsy (CP) to treat lower limb spasticity. There is moderate-quality evidence that in the short term (follow-up 2 to 8 weeks) BoNT-A was more effective than placebo in improving gait scores (RR 1.66; 95% CI, 1.16 to 2.37; p=0.006; 4 randomized controlled trial [RCTs]).[4] Benefits were also seen in medium-term follow-up (12 to 18 weeks). Adverse events (AEs) were similar between groups.
- A Cochrane Systematic Review evaluating treatments for cervical dystonia (CD) in adults found moderate-quality evidence that BoNT-A was more effective at reducing symptoms of CD (based on Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] total score) at 4 weeks with a mean difference [MD] of 8.09 points higher with placebo (95% CI, 6.22 to 9.96).[5] This minimal clinically significant difference (MCID) is 12 points; therefore, this effect was not considered clinically significant. Other outcomes, including health related quality of life, were also improved with the use of BoNT-A compared to placebo.
- There is low-quality evidence from one trial in adult participants, reviewed by CADTH, that the use of incobotulinum toxin A is more effective than placebo for the treatment of sialorrhea associated with neurologic disorders based on salivary flow.[6]
- A Cochrane review found moderate quality evidence that a one-time BoNT-A injection is more effective than placebo in reducing the severity of blepharospasms.[7]
- There is high-quality evidence that the use of BoNT-A for the treatment of migraine is more effective than placebo for reducing the number of headache days per month, in adults with chronic migraine, by a mean decrease of 1.9 days (95% CI, -2.7 to -1.0; 2 RCTs) based on a review by Cochrane Database for Systematic Reviews.[8] There is insufficient evidence that the use of BoNT-A is effective for improving episodic migraine.
- The use of BoNT-A is recommended by National Institute for Health and Care Excellence (NICE) as an option for the management of overactive bladder (OAB) in women with urinary incontinence (UI) and pelvic prolapse who have not responded to pharmacotherapy.[9]
- New evidence from five RCTs support new indications for abobotulinum toxin A (e.g., upper limb spasticity in pediatric patients), onabotulinum toxin A (e.g., upper limb spasticity in pediatric patients, lower limb spasticity in pediatric patients, and pediatric neurogenic detrusor overactivity) rimabotulinum toxin B (e.g., chronic sialorrhea in adults) and incobotulinum toxin A (e.g., chronic sialorrhea in patients 2 years of age and older, upper limb spasticity in pediatric patients, chronic sialorrhea in adults).
- There is moderate-quality evidence that new agent, daxibotulinum toxin A (DAXIFY), is effective in improving glabellar lines (not covered by OHP) based on evidence from two trials.[10] There are no direct or indirect treatment comparisons to other BoNT-A therapies.

Conditions treated with BoNT that lacked conclusive evidence of effectiveness:

- A 2019 review done by Cochrane found that there is very low-quality evidence that BoNT-A improved idiopathic toe walking (ITW) in children (relative risk [RR] 1.21; 95% CI, 0.57 to 2.55; p<0.05).[11]
- There is very low-quality evidence that BoNT-A reduces symptoms of CD in adults more than trihexyphenidyl based on a Cochrane Systematic Review.[12]
- A Rapid Response Review by CADTH found very low-quality evidence for the use of BoNT-A, compared to placebo, reduces symptoms of pelvic pain in women.[13]
- An evidence review from NICE found very low-quality evidence that BoNT-A was more effective than placebo for elucidating a positive response when used for spasticity in people with multiple sclerosis (MS).[14] The recommendation by NICE is that BoNT-A only be used by a specialist due to a lack of high-quality data.[14]

For most indications there was a lack of high-quality evidence for the use of botulinum toxin in children and adolescents. For UI there was insufficient evidence for the use of BoNT-A in a subgroup analysis of older women.

Recommendations:

- Update PA criteria to allow for coverage of BoNT products under the EPSDT program for persons under 21 years of age that is consistent with high-quality evidence.
- No changes to the preferred drug list (PDL) are recommended based on the review of the evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- Botulinum toxins used for migraines were reviewed in May of 2019 and at that time there were no changes to the PDL.
- The PA criteria for chemodenervation using botulinum toxin for the treatment of chronic migraine was updated in September 2018, to cover botulinum toxins for patients with migraine headache that have failed treatment with anticonvulsants, tricyclics and beta-blockers. Renewal of botulinum toxin therapy requires a 7 day or more reduction in headaches from baseline headache frequency. Treatment is limited to two injections given three months apart.
- A list of preferred treatment options is available in Appendix 2.
- Botulinum toxins are administered by a provider and are therefore classified as physician administered drugs (PADs). In the 4th quarter of 2022, there was a small number of claims for BoNT. All botulism products are listed in Appendix 1 and are required to go through prior authorization criteria to ensure use for an approved diagnosis.

Background:

Botulinum toxin works by blocking acetylcholine release at the neuromuscular junction, preventing muscular contraction.[15] Botulinum toxin is available in two serotypes, botulinum toxin type A and botulinum toxin type B. There are four Food and Drug Administration (FDA) approved BoNT-A products and one BoNT-B product currently available. The different botulinum toxin preparations are not interchangeable and potencies are specific for the different formulations. A list of approved BoNTs and their indications are listed in **Table 1**. Botulinum toxin lasts for three to six months dependent upon indication. **Table 2** describes requirements for BoNT coverage for OHP FFS patients as determined by the Health Evidence Review Commission (HERC) and outlined on the Prioritized List of Health Services.

Table 1. FDA Approved Botulinum Products

Generic Name	Brand Name	FDA Indication
Onabotulinum toxin A[16]	BOTOX BOTOX COSMETIC	• Overactive bladder with symptoms of urge incontinence, urgency and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication. • Urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Treatment of neurogenic detrusor overactivity in pediatric **patients 5 years** of age or older who have an inadequate response to or are intolerant of an anticholinergic medication • Prophylaxis of headache in adults with chronic migraine (15 or more days per month with headache lasting 4 hours a day or longer) • Treatment of spasticity in **patients 2 years** of age and older • Treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain • Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients • Treatment of blepharospasm associated with dystonia in **patients 12 years** of age and older • Treatment of strabismus in **patients 12 years of age and older**
Abobotulinum toxin A[17]	DYSPORT	• Cervical dystonia in adults • Temporary improvement in the appearance of moderate to severe glabellar lines associated with the procerus and corrugator muscle activity in adults < 65 years of age • Treatment of spasticity in **patients 2 years** of age and older
Incobotulinum toxin A[18]	XEOMIN	• Chronic sialorrhea in **patients 2 years** of age and older • Upper limb spasticity in adults • Upper limb spasticity in pediatric **patients 2 to 17** years of age, excluding spasticity caused by cerebral palsy • Cervical dystonia in adults • Blepharospasm in adults • Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults
Prabotunlinum toxin A[19]	JEUVEAU	• Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Rimabotulinum toxin B[20]	MYOBLOC	• Cervical dystonia to reduce severity of abnormal head position and neck pain associated with cervical dystonia in adults • Chronic sialorrhea in adults
Daxibotulinum toxin A[10]	DAXXIFY	• Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

Clinical conditions that are treated with BoNTs include neuromuscular disorders (e.g., strabismus, blepharospasm, dystonia, spasticity), urinary disorders (e.g., neurogenic urologic disorders and symptoms of refractory urinary incontinence, urgency and/or frequency), sialorrhea and pain syndromes (e.g., migraine) (**Table 2**).[21] In addition to approved uses, BoNTs are commonly used off-label for many indications, some include: dystonia, ophthalmology indications, pelvic and bladder pain, otorhinolaryngology, and gastroparesis.

Adverse events reported with BoNT include respiratory, speech or swallowing difficulties that may lead to death. Botulinum toxins should be used cautiously in individuals that may have compromised respiratory function or dysphagia. There have been cardiovascular adverse events reported that may occur and potentially lead to death; therefore caution should be used in treating individuals with cardiovascular disease. An enhanced effect of BoNT may be seen in those with underlying neuromuscular disorders. Increased risk of urinary tract infections has been reported when BoNT is used for the treatment of OAB as well as urinary retention. There is a potential for bronchitis and upper respiratory infection when using BoNT for spasticity. All BoNT products have a boxed warning for the risk of spread from the area of injection to produce local and systemic symptoms of botulinum toxin effects. The symptoms have been seen hours to weeks after injection which may result in life threatening swallowing and breathing difficulties and even of death.[16] These AE are more likely to occur in children treated for muscle spasticity; however they can occur in adults and more likely if they have conditions that may predispose them to these AE.[16]

The main outcomes used to determine the efficacy and clinical impact of botulinum toxins are dependent upon the disease state being treated. **Table 2** describes the different indications for which BoNT is used, as well as the most common outcome assessment metric and associated minimal clinically important difference if available. **Table 2** also outlines requirements for BoNT coverage for OHP FFS patients as determined by the Health Evidence Review Commission (HERC) and outlined on the Prioritized List of Health Services.

Table 2. Indications for Botulinum Therapy with Associated Outcomes and Coverage under the Oregon Health Plan

Indication	Outcome Assessment	Prioritized List of Health Services Coverage*
Cervical Dystonia[12,22] • Movement disorder characterized by disabling, painful muscle contractions of the neck • BoNT-A is recommended as a first-line treatment	Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) • Range 0-85, higher is worse • 12 point change is considered the MCID[23] Tsui Scale • 6 item scale accessing involuntary neck movement • Scores range from 1-25 • MCID not determined	Line 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD10-CM G24.9).
Spasticity[24] • Abnormal increase in muscle tone or stiffness • Standard therapy is occupational and/or	Ashworth Scale • Scale ranges from 0-4 (4 is more rigid) • MCID is a change of 1 point or more	Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS Chemodenervation with botulinum toxin injection (CPT 64642-64647) is included on this line for treatment of upper and lower limb spasticity (ICD-10-CM codes G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83)

physiotherapy with antispasticity pharmacotherapy	Global Impression of Change Scale (GICS) • scale ranges from -3 to +3 (higher is better)	
Overactive bladder[25] (Neurogenic detrusor overactivity / Urinary incontinence) • Associated with urgency, frequency and with or without incontinence • First-line therapy recommendations include antimuscarinics	Overactive bladder symptom score (OABSS) • Scores range from 0-15, with higher scores indicating more symptoms • A decrease of 3 points is the MCID	Line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic or beta-3 adrenergic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium, mirabegron, vibegron). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. Positive response to therapy is defined as a reduction on of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency.
Sialorrhea[6] • Excessive drooling often due to a neurologic disorder	There are no validated outcome measures with MCIDs	Not covered – falls below line 472. Line 500 SIALOLITHIASIS, MUCOCELE, DISTURBANCE OF SALIVARY SECRETION, OTHER AND UNSPECIFIED DISEASES OF SALIVARY GLANDS Chemodenervation with botulinum toxin injection (CPT 64611) is included on this line for the treatment of excessive salivation. (ICD-10 -CM K11.5-K11.9,R68.2)
Blepharospasm[7] • Focal dystonia characterized by involuntary eyelid closure • Botulinum toxin is considered first-line therapy	Jankovic Rating Scale (JRS) severity subscore • Values of 0-4 with lower values being better • MCID not determined Patient Evaluation of Global Response (PEGR) • Values of -4 to +4 with higher scores suggesting benefit • MCID not determined	Line 362 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM Chemodenervation with botulinum toxin injection (CPT 64612, 64616) is included on this line only for treatment of blepharospasm (ICD-10-CM G24.5), spasmodic torticollis (ICD-10-CM G24.3), and other fragments of torsion dystonia (ICD10-CM G24.9).
Strabismus • Misalignment of the eye	Correction of eye alignment	Line 351 STRABISMUS DUE TO NEUROLOGIC DISORDER Chemodenervation with botulinum toxin injection (CPT 67345) is included on this line for the treatment of strabismus due to other neurological disorders (ICD-10-CM H50.89).

• Managed with corrective lenses, eye exercises, surgery or botulinum injection		
Migraine Headaches[26] • Moderate to severe headache attacks • First-line treatment options include: beta-blockers, anticonvulsants and tricyclic antidepressants • Botulinum is indicated for chronic migraine headaches	Migraine frequency Migraine Disability Assessment Score (MIDAS) • Scores of 0-5 are indicative of little or no disability, 6-10 mild disability, 11-20 moderate disability, and 21 or greater as severe disability. • MCID is 4.5 points	Line 410 MIGRAINE HEADACHES Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria: A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (e.g. beta-blocker, anticonvulsant or tricyclic antidepressant) C) their condition has been appropriately managed for medication overuse D) treatment is administered in consultation with a neurologist or headache specialist. Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.
Reduction in moderate to severe glabellar lines	Improved appearance	Not a covered indication.
Esophageal stricture • Trouble swallowing • Narrowing of the esophagus	Not FDA approved for this indication	Covered by OHP: Line 378 ESOPHAGEAL STRICTURE; ACHALASIA Chemodenervation with botulinum toxin injection (CPT 43201) is included on this line for treatment of achalasia (ICD-10 K22.0).
Abbreviations: BoNT-A = botulinum toxin A; FDA = Food and Drug Administration; MCID = minimal clinically important difference; NA = not applicable; OHP = Oregon Health Plan. Key: * As determined by the Health Evidence Review Commission (HERC) Guideline Notes for February 1, 2023 Prioritized List of Health Services.		

Additional botulinum toxin indications not covered by the HERC Prioritized List due to lack of evidence:

- Guideline Note 37, surgical interventions for conditions of the back and spine other than scoliosis
- Guideline Note 145, treatments for benign prostate enlargement with lower urinary tract symptoms
- Line 517 disorders of sweat glands, chemodenervation with botulinum toxin injection (CPT 64650, 64653) is included on this line for the treatment of axillary hyperhidrosis and palmar hyperhidrosis (ICD-10-CM L74.52, R61).
- Line 526 chronic anal fissure, chemodenervation with botulinum toxin injection (CPT 46505) is included on this line for the treatment of anal fissures.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence

(NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

AHRQ – Nonsurgical Treatments for Urinary Incontinence in Women

In 2018 AHRQ updated 2012 guidance for the treatment of UI in women.[1] A total of 233 studies were included. Community-dwelling women who were not pregnant with symptoms of UI were included in the eligible population. Study participants were women between the ages of 33 and 85 years old (median age of 55 years).[1] Nonpharmacological, pharmacological and combination therapies were included in the analysis. Pharmacological treatment options included the following: anticholinergics, BoNT-A, hormones (e.g., estrogens), alpha agonists, beta agonists, antidepressants, and periurethral bulking agents. The main outcomes of interest were cure (or complete resolution) of UI symptoms (incontinence, urgency and frequency). For the purpose of this review the use of BoNT-A for UI will be presented.

Onabotulinum toxin A is considered a third-line treatment for UI. Two studies evaluated BoNT-A for urgency UI and reported cure rates. BoNT-A was found to be more effective than no treatment (OR 4.9; 95% CI, 2.82 to 8.65) (high-quality evidence).[1] Evaluation of all types of UI (two studies) found BoNT-A to be superior to no treatment for cure rates (OR 5.67; 95 CI, 2.80 to 11.4) (high-quality evidence). There was low quality evidence that BoNT-A had similar efficacy cure rates as neuromodulation for all types of incontinence and urgency UI, RR 1.69 (95% CI, 0.80 to 3.62) and RR 1.68 (95% CI, 0.80 to 3.55) ($P \geq 0.80$ for both).[1] Evidence summary of efficacy found BoNT-A to be associated with a 43.6% cure rate in women with urgency UI. There was insufficient evidence for the use of BoNT-A in a subgroup analysis of older women (>65 years). Overall, the risk of bias was considered low across all the studies.

In women with urgency UI, indirect evidence found BoNT-A to be more effective than no treatment (OR 3.6; 95% CI, 1.8 to 7.3) based on high-quality evidence.[1] There were no direct comparisons of third line treatment options. The overall percent of women who found improvement with BoNT-A for urgency UI was 66.6%.[1] Low strength of evidence found BoNT-A to be more effective than neuromodulation for achievement of patient satisfaction in women with UI (OR 1.3; 95% CI, 0.93 to 2.1).[1] Overall, 85.5% of women were satisfied with BoNT-A when used for urgency UI.[1]

Thirty-eight percent of women experienced a treatment related AE when treated with BoNT-A for UI. Urinary tract infections (UTI) were the most common AE which occurred in 35% of women receiving BoNT-A (moderate-quality of evidence).[1] There was moderate-quality of evidence that BoNT-A was associated with urinary retention or voiding dysfunction in 18% of women.[1]

Limitations to this systematic review include: the inclusion of direct and indirect evidence, small number of trials available for analysis, small sample size and lack of evidence in subgroup populations, such as women over the age of 65 years.

CADTH – Intravesical Botulinum Toxin for Adults with Non-Neurogenic Bladder Conditions

A CADTH rapid response clinical effectiveness review evaluated BoNT-A for the treatment of non-neurogenic bladder conditions (e.g. OAB, idiopathic detrusor activity, and bladder pain).[2] Literature was searched till February 2019, which identified four systematic reviews, three RCTs and four guidelines. Participants in the studies were adults with a diagnosis of OAB or BPS/IC.

There was high quality evidence that BoNT-A 100 units, compared to placebo or compared to anticholinergics (e.g., solifenacin, oxybutynin, fesoterodine, trospium, darifenacin, tolterodine) improved urgency episodes associated with OAB.[2] Botulinum toxin A (100 to 500 U) reduced pelvic pain in people with BPS/IC compared to placebo based on high quality evidence. Guidelines recommend BoNT-A as a third-line agent, after pharmacotherapy, for OAB based on moderate to high quality evidence. Guidelines recommend BoNT-A for the treatment of BPS/IC for people who are refractory to other treatments (weak strength of evidence).[2] Adverse events of BoNT-A were an increased incidence of urinary tract infections (UTIs) and urinary retention compared to placebo.

Treatment for Sialorrhea (excessive saliva) in People with Motor Neuron Disease/Amyotrophic Lateral Sclerosis

A 2022 Cochrane Review evaluated the use of BoNT A and B in people with sialorrhea as a result of MND (e.g., ALS).[3] Other treatments studied were dextromethorphan hydrobromide, quinidine sulfate and scopolamine; however only results for botulinum toxins will be presented. Four trials (n=110) in patients with MND were included. Participants were 21-85 years of age. Studies were considered to be at low risk of bias.

Normal daily salivary production ranges from 0.5 liters (L) to 1.0 L.[3] The use of BoNT-B was compared to placebo in one small study of 20 people. At eight weeks BoNT-B was found to decrease salivary production by -0.50 mL/5 min (95% CI, -1.07 to 0.07) (moderate quality evidence).[3] Patient reported improvements in sialorrhea symptoms when treated with BoNT-B compared to placebo but results were not statistically significant and based on very low quality of evidence. There was low quality of evidence that BoNT-B may improve quality of life compared to placebo based on the Schedule for Evaluation of Individual Quality of Life direct weighting scale. Adverse events were similar between BoNT-B and placebo, based on low quality of evidence.

A pilot study in 20 people evaluating BoNT-A compared to placebo provided very low quality evidence that there was not a clinical benefit with active treatment.[3]

Limitations to the evidence are lack of large, high-quality trials with objectively measured outcomes. Authors concluded that the evidence was too uncertain to drawn firm conclusions on the role of BoNT-A for sialorrhea.

Cochrane – Interventions for Idiopathic Toe Walking

In 2019 Cochrane reviewed the evidence for the use of interventions in children with ITW.[11] Only one study was included that involved 46 participants who had an average age of 5.1 years. Botulinum toxin was injected bilaterally at a dose of 12 U/kg body weight. The main outcome was improvement in toe walking, defined as parent-reported toe walking less than 50% of the time.

The use of BoNT-A with conservative treatment (e.g., casting below the knee for four weeks) was more effective than conservative treatment alone based on one trial with very low quality evidence (RR 1.21; 95% CI, 0.57 to 2.55; follow-up at 12 months).[11] This benefit was not demonstrated with the use of BoNT-A passive ankle joint dorsiflexion range of movement on the right with the knee extended, on the right with the knee flexed or on the left with the knee extended. There was no demonstrated benefit of BoNT-A on recurrence of toe-walking gait (MD 0.34; 95% CI, -0.09 to 0.78) based on very low quality evidence.[11] There was very low quality evidence that there was no treatment discontinuations due to treatment.

The evidence was based on an open-label study design and therefore subject to a high risk of bias. There is insufficient evidence to support the use of BoNT-A for ITW in children.

Cochrane – Botulinum Toxin Type A in the Treatment of Lower Limb Spasticity in Children with Cerebral Palsy

Cochrane Systematic Reviews evaluated the use of BoNT-A for children who are diagnosed with CP and have lower limb spasticity.[4] Botulinum toxin A was compared to usual care/physiotherapy, placebo or sham treatment, serial casting, or orthoses (external devices). Children were birth to 19 years of age, the mean age was three to seven years old and a majority were males.[4] Most participants had more than one motor type of CP. Thirty-one trials (n=1508) were included. The primary outcome was gait analysis and function measured at 3 time points: short-term follow-up (2 to 8 weeks), medium term follow-up (12 to 16 weeks) and long term follow-up (>24 weeks).

Authors rated the studies as having a high or unclear risk of bias mostly due to blinding concerns introducing performance and detection bias.[4] Comparisons of BoNT-A to usual care/physiotherapy were based on very low quality evidence. Function scores at 2 to 8 weeks were found to be more improved with the use of BoNT-A compared to usual care/physiotherapy (SD 0.59; 95% CI, 0.23 to 0.95; 2 RTCs), which is considered a moderate effect to treatment.[4] Range of motion was found to be slightly improved with BoNT-A compared to usual care/physiotherapy; however, the difference was small and there was high heterogeneity across trials. Spasticity was found to be similar between groups with the use of BoNT-A compared to usual care/physiotherapy (SD 1.19; 95% CI, 2.62 to 0.24).[4] Adverse events were higher in those treated with BoNT-A with 0.37 proportion in the BoNT-A group experiencing an event.

Efficacy comparisons between BoNT-A and usual care/physiotherapy done at a follow-up of 12 to 16 weeks were based on very low-quality evidence. Observational gait score was higher in the BoNT-A group (MD 2.80; 95% CI, 1.55 to 4.05; 1 RCT).[4] Function was improved with BoNT-A compared to usual care/physiotherapy (SD 1.04; 95% CI, 0.16 to 1.91) based on four studies and was associated with high heterogeneity. The difference was considered to be a large effect. Botulinum toxin A was associated with more improvement in range of motion (6.36 degrees; 95% CI, 4.03 to 8.69; passive ankle dorsal flexion; 5 trials).[4] Spasticity was lower in participants treated with BoNT-A compared to usual care/physiotherapy by a decrease in symptoms of a standard mean difference of 1.66 (95% CI, 2.88 to 0.43; 3 RCTs), which was considered a large effect.[4]

Short term (follow-up 2 to 8 weeks) found BoNT-A to be more effective than placebo or sham in improving gait scores based on moderate quality evidence (RR 1.66; 95% CI, 1.16 to 2.37; p=0.006; 4 RCTs).[4] Gait improvements were also seen at medium-term follow-up (12 to 18 weeks) in participants receiving BoNT-A compared to placebo or sham (RR 1.90; 95% CI, 1.32 to 2.74; P<0.001; 3 RCTs).[4] Short-term follow up demonstrated improvements in peak ankle dorsiflexion in stance and swing, based on moderate evidence, mean difference 15.90 (95% CI, 4.87 to 26.93; p=0.005) and mean difference 10.20 (95% CI, 4.01 to 16.39; p=0.001), respectively.[4] Function scores were not improved with BoNT-A compared to sham or placebo in the short or long term; however a small effect was demonstrated in the medium term (SMD 0.28; 95% CI, 0.06 to 0.49; P=0.01; 5 RCTs) (moderate quality evidence).[4] Adverse events were similar between groups at short-term follow up visits (moderate strength of evidence).

There was no difference between the use of BoNT-A and serial casting for short, medium, long-term follow up for most outcomes based on one RCT (moderate quality of evidence). Instrumental gait analysis (ankle dorsiflexion at initial contact) was improved with BoNT-A compared to serial casting (MD 6.59 degrees; 95% CI, 1.39 to 11.78; P=0.01; 2 RCTs) (moderate quality of evidence).[4] Low quality evidence found no difference in incidence of adverse events.

Very low quality evidence found BoNT-A was more effective than orthoses at improving hip range of motion and hip adductors spasticity; however function was not improved at medium term follow up.[4]

All trials included in the analysis were small and of limited duration. The quality of evidence was determined to be very low quality for many outcomes and additional high-quality studies are needed.

Cochrane – Botulinum Toxin Type A for Cervical Dystonia

Cochrane performed a systematic review and evidence evaluation for the treatments for CD in adult patients.[5] Nine RCTs (n=1144) comparing a single BoNT-A treatment to placebo were included in the review. The mean age was 52.8 years and 64% were female. Duration of CD ranged from 4.8 years to 12.1 years and severity of CD was moderate to severe (TWSTRS score of 13.9 to 14.4). Types of BoNT-A included: 150 units to 500 units onabotulinum toxin A (BOTOX), 120 units to 240 U of incobotulinum toxin A (XEOMIN), and 250 units to 1000 units abobotulinum toxin A (DYSPORT).[5] The primary outcome of interest was CD improvement as assessed by TWSTRS score (range 0-85, higher values equated with worse symptoms). Outcomes were assessed at 4-6 weeks.

The authors determined the overall risk of bias to be moderate for the included studies. BoNT-A was more effective at reducing symptoms of CD (based on TWSTRS total score) at 4 weeks with a MD of 8.09 points higher with placebo (95% CI, 6.22 to 9.96) (moderate quality evidence).[5] Subjective participant assessment of symptoms was much improved in those treated with BoNT-A compared to placebo (RR 2.19; 95% CI, 1.78 to 2.70), based on high-quality evidence. Pain due to CD was lower in those treated with BoNT-A with a MD of 2.11 points increase in those treated with placebo (based on TWSTRS pain scale, 0-20 with higher scores worse) (moderate quality evidence). There were a higher number of dropouts in those treated with BoNT-A compared to placebo, based on high quality evidence (RR 0.48; 95% CI, 0.32 to 0.73).[5] Health related quality of life was higher in participants treated with BoNT-A compared to placebo, based on moderate quality evidence). There was moderate quality evidence that AEs were higher in those treated with BoNT-A (RR 1.23; 95% CI, 1.05 to 1.43).[5]

Limitations included the exclusion of patients with a previous poor response to BoNT-A in participating in seven of the nine studies.

Cochrane – Botulinum Toxin Type A versus Anticholinergics for Cervical Dystonia

Cochrane updated a 2005 review in 2021 on the management of CD with BoNT-A, which is considered first-line treatment.[12] Trials comparing BoNT-A to anticholinergics were included. Only one trial was identified, which included 66 adult participants with an average age of 50.7 years. The severity of CD was moderate, average TWSTRS score of 15.9. Two doses of BoNT-A, abobotulinum toxin A 262 units (week 8) and 292 units (week 0) were compared to trihexyphenidyl, up to 24 mg daily.[12] All participants were BoNT-A naïve. The primary outcome was measurement of CD symptoms by the TWSTRS.

The trial was rated as having moderate risk of bias due to multiple domains that had uncertain risk of bias. At 12 weeks, BoNT-A reduced CD severity by 2.5 points (95% CI, 0.68 to 4.32) compared to trihexyphenidyl (very low quality evidence).[12] There were 31 adverse events in the BoNT-A group compared to 76 events in those treated with trihexyphenidyl. There was less dry mouth and memory problems in those treated with BoNT-A compared to trihexyphenidyl. Additional studies are needed to determine the comparative efficacy of BoNT-A to anticholinergics.

CADTH – Injectable Botulinum Toxin for Pelvic Pain

Botulinum toxin for use in women with pelvic pain was evaluated by CADTH in a 2019 rapid response review.[13] A literature search up to July of 2019 identified three RCTs and two systematic reviews to provide evidence for the use of BoNT-A for pelvic pain (BoNT-B was not studied). Adult patients, 18 years and older, with pelvic floor pain due to vulvodynia, vaginismus, endometriosis and short pelvic floor syndrome were included. Bladder conditions were excluded. Patients included in the systematic reviews were a mean age of 26 years and those in the RCTs ranged from a median of 27 to 42 years.[13]

Findings from one of the systematic reviews found transvaginal BoNT-A (50-300 U) effective for dyspareunia with a decrease of 2.3-4.47 points in the 10-point visual analog scale (VAS) compared to placebo, which is higher than the MCID (low quality evidence; cohort studies).[13] Patients with vestibulodynia did not show benefit with BoNT-A treatment. A second systematic review found no difference between BoNT-A and placebo for vaginismus, including BoNT-A injections, behavioral sex therapy, cognitive behavioral therapy (CBT), pharmacological therapy, pelvic floor physiotherapy, and removal of hymenal remnants.

A RCT found that BoNT-A was not more effective in decreasing muscle pain compared to placebo.[13] A small study found no difference between BoNT-A 50 U, BoNT-A 100 U and placebo in pain, based on VAS, at three months. A third, small (n=58) RCT found physiotherapy was more effective than BoNT-A for improvements in sexual function.[13] Additional, high-quality evidence is needed to support the use of BoNT-A for pelvic pain.

Limitations to the evidence include limited external validity with the enrollment of specific groups of participants (e.g., highly educated, failed other treatments and those with severe pain). Many outcomes were self-reported by patients and may be prone to recall bias.

CADTH – Incobotulinum toxin A Reimbursement Review

The Canadian Agency for Drugs and Technology in Health reviewed the use of incobotulinum toxin A for the treatment of moderate to severe chronic sialorrhea associated with neurologic disorders.[6] Recommendations for use were based on a review of one clinical trial (n=184) comparing incobotulinum toxin A 100 U to placebo in adult patients that demonstrated reduction in salivary flow with the use of incobotulinum toxin A (SIAXI[27]; trial details available in **Table 3**).

After review of the evidence, CADTH recommends that incobotulinum toxin A should be an option for the treatment of moderate to severe chronic sialorrhea associated with neurologic disorders if the following criteria are met:[6]

- In the care of a specialist with experience in managing neurologic conditions
- Sialorrhea lasting for at least 3 months or more
- Drooling severity and frequency scale (DSFS) sum score of 6 or greater and frequency and severity score of 2 or more
- No evidence of dysphagia
- Initial authorization of 16 weeks (dose of 100 units at interval of at least 16 weeks or longer is recommended)
- Renewals are recommended for those people who have a reduction in frequency and/or severity of sialorrhea

Cochrane – Botulinum Toxin Type A Therapy for Blepharospasms

The efficacy of BoNT-A in the management of blepharospasms was the focus of a 2020 Cochrane systematic review.[7] Three RCTs were identified enrolling a total of 313 participants with a mean age of 61.2 years and 66% female. All studies evaluated a one-time treatment of BoNT-A at 4 to 6 weeks after injection.[7] Studies enrolled people with moderate to severe blepharospasm impairment. The primary outcome was symptom improvement using validated measurements (e.g., JRS severity subscore).

The trials were considered to be at low to moderate risk of overall bias. Botulinum toxin A was compared to placebo and was found to reduce blepharospasm-specific severity (measured by the JRS severity scale) by a mean difference of 0.93 (95% CI, 0.61 to 1.25) based on moderate strength of evidence.[7] Subjective participant evaluation (measured by the Patient Evaluation of Global Response [PEGR]) was higher (more effective) in those treated with BoNT-A compared to placebo (SMD 0.86; 95% CI, 0.53 to 1.2) based on high quality evidence. Low quality evidence from two RCTs found BoNT-A to be more effective at reducing the frequency of blepharospasm-specific involuntary movements when compared to placebo (SMD 0.79; 95% CI, 0.31 to 1.27). One trial found the duration of BoNT-

A to last an average of 10.6 weeks (moderate quality of evidence). Adverse events were similar with BoNT-A compared to placebo (RR 1.18; 95% CI, 0.87 to 1.60) (low quality of evidence).[7]

Limitations include two of the trials excluding individuals with a prior history of poor response to BoNT-A, selecting out responders to therapy.

Cochrane – Botulinum toxins for the Prevention of Migraine

A 2018 Cochrane Systematic Review evaluated the evidence for the use of BoNT-A in adult patients with chronic or episodic migraine in adults.[8] Twenty-eight studies were included, with 4190 participants. The mean age was 42 years old and 85% were women. Eleven trials allowed Concomitant prophylactic medications at stable doses. Migraine severity ranged from mild to severe. The main outcomes were number of migraine days a month and global disease impact. The global disease impact was measured by the Migraine Impact and Disability Assessment Score (MIDAS).

The overall quality of evidence was considered very low all trials (episodic and chronic).[8] Only one trial evaluated the use of BoNT for episodic migraine and found no difference between BoNT-A and placebo (p=0.49) for the number of migraine days per month.[8]

The use of BoNT-A was compared to placebo in 23 trials as a preventative treatment for chronic migraine. There was high quality evidence that the use of BoNT-A reduced the number of headache days per month in those with chronic migraine by a mean decrease of 1.9 days (95% CI, 2.7 to 1.0 lower).[8] The number of migraine days per month in those with chronic migraine was also decreased with BoNT-A compared to placebo (MD 3.1; 95% CI, 4.7 to 1.4) (low quality evidence). Adverse events were higher in participants treated with BoNT-A compared to placebo based on moderate quality of evidence (RR 1.28; 1.12 to 1.47; 13 RCTs).[8]

In a comparison of BoNT-A to prophylactic therapy for migraine prevention (e.g., topiramate) found very low-quality evidence that there was no difference between groups for the number of migraine days per month in those with chronic migraine. The use of BoNT-A did result in one less headache day per month compared to topiramate (MD 1 day; 95% CI, -4.3 to 2.3 days; p>0.05); however, the results are not statistically signficant.[8] The MIDAS score was 4.3 points higher (95% CI, -28 to 37) in those treated with BoNT-A compared to topiramate (very low quality evidence).[11]

The quality of evidence was low to very low for many outcomes, thus limiting conclusions on overall effectiveness for BoNT-A in chronic migraine. There is a need for more high-quality trials comparing BoNT-A to other chronic migraine preventative therapies to adequately determine the place in therapy for BoNT-A in treating migraine.

After review, 12 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[28–35,36–39]

New Guidelines:

High Quality Guidelines:

NICE – Urinary Incontinence and Pelvic Organ Prolapse in Women

Guidance on the treatment of UI and pelvic organ prolapse in adult women was updated in 2019.[9] NICE recommends nonsurgical management and oral medication for treating overactive bladder, which is often the cause of incontinence. Invasive procedures can be offered to people who continue to have symptoms despite nonsurgical management or treatment with medications. In people with detrusor overactivity, leading to OAB symptoms, NICE recommends

bladder wall injection with BoNT-A if the patents has not responded to non-surgical measures, including pharmacotherapy.[9] In women with OAB that is not caused by detrusor overactivity and symptoms have not responded to non-surgical management BoNT-A is recommended as an option. All women should be advised that the use of BoNT-A may result in increased risk of UTIs and need for intermittent catheterization due to voiding dysfunction. There is insufficient evidence on the long-term use of BoNT-A for UI.

Initial dosing of BoNT-A for overactive bladder is 100 units.[9] If additional doses are required, 200 units of BoNT-A 12 weeks later can be used. It is recommended that if symptoms improved initially but were not sustained until 6 months with a 100 units of BoNT-A, a dose of 200 units should be offered at 12 weeks. The use of botulinum toxin B is not recommended for OAB.

NICE – Multiple Sclerosis in Adults: Management

In June of 2022 NICE conducted an evidence review on the pharmacological management of spasticity in people with MS that included evidence from three RCTs comparing botulinum to placebo.[14] Included patients were 18 years of age or older. Participants were allowed to take stable antispasticity medications and analgesic medications. Patients had baseline Modified Ashworth Scores (MAS) of 8.5 to 16, Expanded Disability Status Scale (EDSS) scores greater than 7 and history of having MS for 12.9 to 22.9 years.[14] Trials were small with 74-106 participants in each and outcomes were measured at 4 and 8 weeks. Important outcomes were: spasticity scales (e.g., MAS, Tardieu Scale, Muscle Elastography MS Scale [MEMSs], Fugl Meyer Scale [FMS]), patient reported measures of spasticity (e.g., Penn Spasm Frequency Scale, Numeric Rating Scale for Spasticity (NRS-S), MS Spasticity Scale-88 [MSSS], Patient Reported Impact of Spasticity Measure [Prism], functional scales (e.g., EDSS), health related quality of life and adverse events. Outcomes were categorized as three to six months follow-up or greater than six month follow up.

All studies were downgraded due to serious concerns with imprecision. All efficacy outcomes were based on very low quality of evidence.[14] A positive response (e.g., MAS, muscle tone and clinical global rating) was higher in those treated with BoNT-A 500, 1000 or 1500 units compared to placebo. Those treated with BoNT-A 500 units demonstrated a positive response in 61.9% of participants compared to 43.8% treated with placebo (RR 1.41; 95% CI, 0.74 to 2.71).[14] Positive response rates were higher for participants treated with 1000 units BoNT-A compared to placebo (RR 1.09; 95% CI, 0.53 to 2.22) and for those treated with 1500 units (RR 1.08; 95% CI, 0.51 to 2.28).[14] There was moderate quality of evidence that BoNT-A was associated with more adverse events compared to placebo (RR 3.71; 95% CI, 1.11 to 12.39). NICE recommends that BoNT-A should only be used if recommended by a specialist due to the lack of clinical evidence.

After review, three guidelines were excluded due to poor quality.[40–42]

New Formulations or Indications:

Abobotulinum toxin A (DYSPORT):

- In September of 2019, abobotulinum toxin A was approved for the treatment of upper limb spasticity in pediatric patients 2 years of age and older, excluding spasticity caused by cerebral palsy.[17] Details and results of the trial used for approval are outlined in **Table 3**.

Onabotulinum toxin A (BOTOX):

- In June of 2019, onabotulinum toxin A received an indication for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age.[16] Approval was based on one unpublished, multi-center, double-blind, placebo-controlled RCT of pediatric patients with upper limb spasticity due to

CP or stroke randomized to onabotulinum toxin A 3 units/kg, 6 units/kg or placebo.[16] The primary endpoint was MAS and the Clinical Global Impression of Overall Change by Physician (CGI), the average of week 4 and 6 for both outcomes. The mean change from baseline in MAS was -1.92, -1.87 and -1.21 for onabotulinum toxin A 3 units/kg, onabotulinum toxin A 6 units/kg and placebo, respectively ($p<0.05$ compared to placebo for both groups).[16] The change in CGI was 1.88, 1.87 and 1.66 for onabotulinum toxin A 3 units/kg, onabotulinum toxin A 6 units/kg and placebo, respectively ($p>0.05$ for all comparisons).

- Onabotulinum toxin A was approved for use for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age.[16] One multi-center, double-blind, placebo-controlled RCT demonstrated the efficacy of onabotulinum toxin A in pediatric patients with CP. The primary endpoint was MAS and the CGI, average of week 4 and 6 for both outcomes. Onabotulinum toxin A 4 units/kg decreased MAS by -1.01 ($p<0.05$), onabotulinum toxin A 8 units/kg by -1.06 and placebo by -0.80. The CGI changed by 1.49, 1.65 and 1.36 for onabotulinum toxin A 4 units/kg, 8 units/kg and placebo, respectively.
- In February 2021 onabotulinum toxin A was approved for the treatment of pediatric neurogenic detrusor overactivity. Details and results of the trial used for approval are outlined in **Table 3.**[43]
- In July of 2021 onabotulinum toxin A was approved for 8 additional upper limb muscles within the approved muscle groups for the adult upper limb spasticity indication.[16]

Rimabotulinum toxin B (MYOBLOC):

- Rimabotulinum toxin B received a new indication for the treatment of chronic sialorrhea in adults in August of 2019.[20] Approval was based off of two studies that were phase 3, double-blind, placebo-controlled RCTS. The first trial studied adult patients with sialorrhea for at least 3 months associated with Parkinson's disease, ALS, stroke or other causes. The co-primary outcomes were unstimulated salivary flow rate USFR and Clinical Global Impression of Change (CGI-C) at week four. A single treatment of rimabotulinum 2,500 units reduced the USFR by -0.37 gram (g)/minute (min), rimabotulinum 3,500 units decreased USFR by -0.36 g/min and placebo decreased USFR by -0.07 g/min.[20] Both doses of rimabotulinum were statistically superior to placebo. The CGI-C was 2.38 for rimabotulinum of 2,500 units, 2.45 for rimabotulinum of 3,500 units and 3.59 for placebo ($p<0.001$ for both doses compared to placebo). The second study was conducted in mostly male, adult patients with Parkinson's disease. At week four, rimabotulinum 1,500 units decreased USFR by -0.44, rimabotulinum 2,500 units decreased USFR by -0.38 ($p<0.001$) and rimabotulinum 3,500 units decreased USFR by -0.30 ($p<0.001$) and placebo increased USFR by 0.01 g/min.[20] CGI-C scores were improved in those participants treated with rimabotulinum 1,500 units, rimabotulinum of 2,500 units and rimabotulinum 3,500 units compared to placebo, 2.14 ($p<0.0001$), 2.00 ($p<0.0001$), 1.62 ($p<0.0001$) and 3.93, respectively.[20]

Incobotulinum toxin A (XEOMIN)

- Incobotulinum toxin A was approved in for the treatment of chronic sialorrhea in patients 2 years of age and older in December of 2020.[18] Approval was based on a double-blind, placebo-controlled trial of patients 6-17 years, patients 2-5 years received open-label treatment. Results were based on patients 6-17 years of age. At week 4, incobotulinum toxin A was more effective than placebo for changes in uSFR and GICS ($p<0.05$).[18]
- In August of 2020 incobotulinum toxin A was approved for treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy. Incobotulinum toxin A was studies in a double-blind, placebo-controlled trial in pediatric patients with upper limb spasticity. At week 4 the changes in AWS were more effective for incobotulinum toxin A 8 units/kg compared to 2 units/kg, which served as the control ($p<0.05$). Changes in the other co-primary outcome, GICS, was not statistically different between groups.[18]
- Incobotulinum received an addition indication in July 2018 for the treatment of chronic sialorrhea in adults.[18] Details and results of the trial used for approval are outlined in **Table 3**.[27]

Daxibotulinumtoxina-lanm (DAXXIFY)

- DaxibotulinumtoxinA-lanm was approved in by the FDA on September 7, 2022 for adult patients for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity. Daxibotulinum toxin A is give as 8 units into five sites for a total dose of 40 units.[10] Evidence used for approval are outlined in **Table 3.** Common adverse reactions are headache, eyelid ptosis, and facial paresis. Like other BoNT products, daxibotulinum has a boxed warning for the risk of spread with the potential to cause swallowing and breathing difficulties which can be life threatening and there have been reports of death. Daxibotulinum toxin is not indicated for the treatment of spasticity.[10]

New FDA Safety Alerts:
No new safety alerts identified.

Randomized Controlled Trials:
A total of 88 citations were manually reviewed from the initial literature search. After further review, 82 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 seven trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Austin, et al[43] DB, MC, Phase 3, RCT	Onabotulinum toxin A 50 units as one dose Onabotulinum toxin A 100 units as one dose Onabotulinum toxin A 200 units as one dose	Children ages 5 to 17 years with NDO and UI	Change from baseline in daytime UI episodes at week 6	Onabotulinum toxin A 50 units: -1.3 episodes/day Onabotulinum toxin A 100 units: -1.3 episodes/day Onabotulinum toxin A 200 units: -1.3 episodes/day	The 50 unit dose was used due to ethical concerns of placebo use in children for this indication. *Onabotulinum toxin was considered to be effective for the treatment of NDO in pediatrics.*
Carruthers, et al[44] SAKURA 1 DB, MC, Phase 3, RCT	Daxibotulinum toxin A 40 units as one dose Placebo	Patients with moderate to severe glabellar lines as measured by the Investigator Global Assessment -	2 or more point improvement in glabellar line severity (as measured by the GAFWAS and PFWS) at maximum frown at week 4	Daxibotulinum toxin A: 298 (73.6%) Placebo: 0% P<0.0001	*Daxibotulinum toxin A was more effective than placebo in reducing glabellar lines.*

		Frown Wrinkle Assessment Scale (GAFWAS) and the Patient Frown Wrinkle Scale (PFWS)			
Carruthers, et al[44] SAKURA 2 DB, MC, Phase 3, RCT	Daxibotulinum toxin A 40 units as one dose Placebo	Patients with moderate to severe glabellar lines	2 or more point improvement in glabellar line severity at maximum frown at week 4	Daxibotulinum toxin A: 151 (74.0%) Placebo: 2 (1.0%) P<0.0001	*Daxibotulinum toxin A was more effective than placebo in reducing glabellar lines.*
Dabrowski, et al[45] DB, MC, Phase 3, RCT	Incobotulinum toxin A 8 units/kg (max dose 200 units/upper limb) Incobotulinum toxin A 6 units/kg (max dose 150 units/upper limb) Incobotulinum toxin A 2 units/kg (control group) (max dose 50 U/upper limb) - Patients had option of entering open-label extension trial. - Stable centrally acting antispastic medication was allowed - Patients could receive unilateral or bilateral lower-limb injections in addition	Children ages 2 to 17 years with unilateral or bilateral spastic CP and Ashworth Scale* (AS) score of 2 or greater (n=372)	Change from baseline at week 4 in the AS score for the main clinical target pattern chosen from flexed elbow or wrist. Co-primary outcome was the investigator's Global Impression of Change Scale+ (GICS) for the upper limb	AS Score: Incobotulinum toxin A 8 units/kg: -1.15 Incobotulinum toxin A 6 units/kg: -1.02 Incobotulinum toxin A 2 units/kg: -0.93 <u>Incobotulinum toxin A 8 units/kg vs. Incobotulinum toxin A 2 units/kg:</u> TD -0.22; P=0.017 (No CI provided) <u>Incobotulinum toxin A 6 units/kg vs. Incobotulinum toxin A 2 units/kg:</u> TD -0.09; P=0.546 (No CI provided) <u>Investigator's GICS score:</u> Incobotulinum toxin A 8 units/kg: 1.64 Incobotulinum toxin A 6 units/kg: 1.44 Incobotulinum toxin A 2 units/kg: 1.55	Difference between groups is considered clinically significant. There was no difference between the doses for the outcome of GICS. Limitations to the study was that there was no placebo-controlled group, small sample size and short study duration. *Greater spasticity improvements were seen in patients treated with incobotulinum toxin A 8 units/kg compared to 2 units/kg*.

	to upper limb injections			P = >0.05 for all comparisons	
Delgado, et al[46] DB, MC, Phase 3, RCT	Abobotulinum toxin A 16 units/kg (maximal total body dose of 640 units) Abobotulinum toxin A 8 units/kg (maximal total body dose of 320 units) Abobotulinum toxin A 2 units/kg (control) (maximal total body dose of 80 U) - All patients also received personalized, goal-oriented home exercise therapy program (HETP)	Children ages 2 to 17 years with CP and Modified Ashworth Score (MAS) of 2 or greater and Gross Motor Function Classification System (GMFCS) of I to IV. (n=210)	Change from baseline in MAS at week 6 of cycle 1	Abobotulinum toxin A 16 units/kg: -2.3 Abobotulinum toxin A 8 units/kg: -2.0 Abobotulinum toxin A 2 units/kg: -1.6 <u>Abobotulinum toxin A 16 units/kg vs. Abobotulinum toxin A 2 units/kg:</u> TD -0.7; P<0.001 (No CI provided) <u>Abobotulinum toxin A 8 units/kg vs. Abobotulinum toxin A 2 units/kg:</u> TD -0.4; P=0.012 (No CI provided)	*Abobotulinum toxin A 8 units/mg and 18 units/kg was effective in treating spasticity associated with CP that was clinically significant.*
Heinen F, et al[47] DB, MC, Phase 3, RCT	Incobotulinum toxin A 4 units/kg (max dose 100 units) Incobotulinum toxin A 12 units/kg (max dose 300 units) Incobotulinum toxin A 16 units/kg (control group) (max dose 400 units)	Children (2-17 years) with lower-limb unilateral or bilateral CP related spasticity and AS plantar flexor (PF) score of 2 or greater (n=311)	Change from baseline in AS-PF score at 4 weeks and co-primary outcome was the investigator's Global Impression of Change Scale+ (GICS)	AS-PF Score: Incobotulinum toxin A 4 units/kg: -0.68 Incobotulinum toxin A 12 units/kg: -0.69 Incobotulinum toxin A 16 units/kg: -0.70 P<0.0001 for all comparison to baseline values <u>GICS-PF score:</u> Incobotulinum toxin A 4 units/kg: 1.5	*Use of incobotulinum toxin A did not result in a clinically significant benefit in lower-limb spasticity despite results being statistically significant*.

				Incobotulinum toxin A 12 units/kg: 1.51 Incobotulinum toxin A 16 units/kg: 1.54 P<0.0001 for all comparisons to baseline values	
Jost W, et al[27] DB, MC, PC, Phase 3, RCT	Incobotulinum toxin A 75 units as a single dose Incobotulinum toxin A 100 units as a single dose Placebo	Adult patients with chronic sialorrhea due to Parkinson's disease, atypical Parkinsonism, stroke or traumatic brain injury (n=184)	Co-primary endpoint of uSFR from baseline and GICS at week 4	Change in USF at 4 weeks: Incobotulinum toxin A 75 units: -0.06 Incobotulinum toxin A 100 units: -0.13 Placebo: -0.04 <u>Incobotulinum toxin A 75 units vs. placebo:</u> LS mean -0.02 (No CI provided) P=0.542 <u>Incobotulinum toxin A 100 units vs. placebo:</u> LS mean -0.09 (No CI provided) P=0.004 <u>Changes in GICS at 4 weeks:</u> Incobotulinum toxin A 75 units: 1.05 Incobotulinum toxin A 100 units: 1.28 Placebo: 0.7 <u>Incobotulinum toxin A 75 units vs. placebo:</u> LS mean 0.35 (No CI provided) P=0.055 <u>Incobotulinum toxin A 100 units vs. placebo:</u> LS mean 0.58 (No CI provided) P=0.002	*Incobotulinum toxin 100 units was effective in reducing the uSFR more than placebo; however, it is unknown if the decrease is clinically significant.*

Key: *Ashworth Scale = five point scale from 0 (no increase in muscle tone) to 4 (limb rigidity in flexion/extension); + Global Impression of Change Scale = seven-point Likert scale from -3 (very much worse) to +3 (very much improved) for the impression of change in spasticity compared to the condition before the last injection.
Abbreviations: AS = Ashworth scale CI = confidence interval; CP = cerebral palsy; DB = double-blind; GICS= Global Impression of Change Scale; kg = kilogram; LS = least squares; MAS = Modified Ashworth Score; MC = multi-center; NDO = neurogenic detrusor overactivity; PF = plantar flexor; RCT = randomized clinical trial; TD = treatment difference; U = units; UI = urinary incontinence; uSFR = unstimulated salivary flow rate.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form
abobotulinumtoxinA	DYSPORT	VIAL
incobotulinumtoxinA	XEOMIN	VIAL
onabotulinumtoxinA	BOTOX	VIAL
onabotulinumtoxinA	BOTOX COSMETIC	VIAL
prabotulinumtoxinA-xvfs	JEUVEAU	VIAL
rimabotulinumtoxinB	MYOBLOC	VIAL
daxibotulinumtoxinA-lanm	DAXXIFY	VIAL

Appendix 2: Abstracts of Comparative Clinical Trials

IncobotulinumtoxinA Efficacy/Safety in Upper-Limb Spasticity in Pediatric Cerebral Palsy: Randomized Controlled Trial
Edward Dabrowski , Marta Banach, Petr Kaňovský, Hanna Dersch, Michael Althaus , Thorin L Geister, Florian Heinen

Background: This randomized phase 3 study with double-blind main period (MP) and open-label extension (OLEX; NCT02002884) assessed incobotulinumtoxinA safety and efficacy for pediatric upper-limb spasticity treatment in ambulant/nonambulant (Gross Motor Function Classification System [GMFCS] I-V) patients, with the option of combined upper- and lower-limb treatment.
Methods: Patients were aged two to 17 years with unilateral or bilateral spastic cerebral palsy (CP) and Ashworth Scale (AS) score ≥2 in treatment-selected clinical patterns. In the MP, patients were randomized (2:1:1) to incobotulinumtoxinA 8, 6, or 2 U/kg body weight (maximum 200, 150, 50 U/upper limb), with optional lower-limb injections in one of five topographical distributions (total body dose ≤16 to 20 U/kg, maximum 400 to 500 U, depending on body weight and GMFCS level). In the OLEX, patients received three further treatment cycles, at the highest MP doses (8 U/kg/upper limb group). Outcomes included AS, Global Impression of Change Scale (GICS), and adverse events (AEs).
Results: AS scores improved from baseline to week 4 in all MP dose groups (n = 350); patients in the incobotulinumtoxinA 8 U/kg group had significantly greater spasticity improvements versus the 2 U/kg group (least-squares mean [standard error] for upper-limb main clinical target pattern -1.15 [0.06] versus -0.93 [0.08]; P = 0.017). Investigator's, child/adolescent's, and parent/caregiver's GICS scores showed improvements in all groups. Treatment benefits were sustained over further treatment cycles. AE incidence did not increase with dose or repeated treatment across GMFCS levels.
Conclusions: Data provide evidence for sustained efficacy and safety of multipattern incobotulinumtoxinA treatment in children and adolescents with upper-limb spasticity.

Efficacy and safety of abobotulinumtoxinA for upper limb spasticity in children with cerebral palsy: a randomized repeat-treatment study
Mauricio R Delgado, Ann Tilton, Jorge Carranza-Del Río, Nigar Dursun, Marcin Bonikowski, Resa Aydin, Iwona Maciag-Tymecka, Joyce Oleszek, Edward Dabrowski, Anne-Sophie Grandoulier, Philippe Picaut; Dysport in PUL study group
Aim: To assess the efficacy and safety of repeat abobotulinumtoxinA injections in reducing upper limb spasticity in children with cerebral palsy (CP).
Method: This was a double-blind, repeat-cycle study (NCT02106351) in children with CP (2-17y). Children were randomized to receive 2U/kg (control), 8U/kg, or 16U/kg abobotulinumtoxinA injections into the target muscle group (wrist or elbow flexors) and additional muscles alongside occupational therapy via a home-exercise therapy program (HETP; minimum five 15min sessions/wk). Children received 8U/kg or 16U/kg plus HETP in cycles 2 to 4.

Results: During cycle 1, 210 children (126 males, 84 females; mean age [SD] 9y [4y 5mo], range 2-17y; n=70/group) had at least one upper limb abobotulinumtoxinA injection and 209 complied with the HETP. At week 6 of cycle 1, children in the 8U/kg or 16U/kg groups had significantly lower Modified Ashworth scale scores versus the 2U/kg group (primary outcome: treatment differences of -0.4 [p=0.012] and -0.7 [p<0.001] respectively). All groups improved on Physician Global Assessment and children in all groups achieved their treatment goals at least as expected. Therapeutic benefits were sustained during cycles 2 to 4; muscular weakness was the only treatment-related adverse event reported in at least one child/group (4.3% and 5.7% vs 1.4% respectively).
Interpretation: Treatment with 8U/kg or 16U/kg abobotulinumtoxinA significantly reduced upper limb spasticity versus the 2U/kg control dose. Therapeutic benefits of abobotulinumtoxinA plus HETP were sustained with repeat treatment cycles.

Long-term Safety and Tolerability of Repeated Treatments With OnabotulinumtoxinA in Children With Neurogenic Detrusor Overactivity
Israel Franco, Piet B Hoebeke, Eric Dobremez, Wilson Titanji, Till Geib, Brenda Jenkins, Irina Yushmanova, Paul F Austin
Purpose: OnabotulinumtoxinA is an approved treatment for neurogenic detrusor overactivity in adults inadequately managed with anticholinergics, and more recently was approved in children on the basis of a phase 3, 48-week, single-treatment study (NCT01852045). Given the paucity of long-term pediatric data, we report on the continued safety in these patients after repeated onabotulinumtoxinA treatment.
Materials and methods: This was a multicenter, double-blind, repeat-treatment extension study (NCT01852058) in patients who entered from the preceding single-treatment study. Data were integrated across both studies. All patients (5-17 years) used clean intermittent catheterization and could receive dose escalations based on response to preceding treatment (50 U, 100 U, or 200 U onabotulinumtoxinA [not to exceed 6 U/kg]).
Results: Overall, 95, 90, 55, and 11 patients received 1, 2, 3, and 4 treatments with onabotulinumtoxinA, respectively, and median (quartiles) duration of follow-up was 82 (65, 94) weeks. The safety profile was similar across doses and after repeat treatments. The most common treatment-emergent adverse event during cycles 1, 2, and 3 was urinary tract infection (31%, 34%, 22%). Three serious treatment-emergent adverse events related to study treatment (3/95; 3.2%) were reported during the study, which were all cases of urinary tract infection. Annualized urinary tract infection rates post-treatment were similar to pre-screening rates. There were no cases of autonomic dysreflexia, neutralizing antibodies, and treatment-emergent adverse events related to distant spread of toxin.
Conclusions: OnabotulinumtoxinA continued to be well tolerated after repeated treatments in pediatric neurogenic detrusor overactivity patients with similar safety profiles across dose groups. Treatment-emergent adverse events were primarily urological with no new safety concerns.

OnabotulinumtoxinA for the treatment of neurogenic detrusor overactivity in children
Paul F Austin, Israel Franco, Eric Dobremez, Pawel Kroll, Wilson Titanji, Till Geib , Brenda Jenkins, Piet B Hoebeke
Aims: This study evaluated whether one (or more) of three doses of onabotulinumtoxinA were safe and effective to treat neurogenic detrusor overactivity (NDO) in children.
Methods: This was a 48-week prospective, multicenter, randomized, double-blind study in children (aged 5-17 years) with NDO and urinary incontinence (UI) receiving one onabotulinumtoxinA treatment (50, 100, or 200 U; not to exceed 6 U/kg). Primary endpoint: change from baseline in daytime UI episodes. Secondary endpoints: change from baseline in urine volume at first morning catheterization, urodynamic measures, and positive response on the treatment benefit scale. Safety was also assessed.
Results: There was a similar reduction in urinary incontinence from baseline to Week 6 for all doses (-1.3 episodes/day). Most patients reported positive responses on the treatment benefit scale (75.0%-80.5%). From baseline to Week 6, increases were observed in urine volume at first morning clean intermittent catheterization (50 U, 21.9 ml; 100 U, 34.9 ml; 200 U, 87.5 ml; p = 0.0055, 200 U vs. 50 U) and in maximum cystometric capacity (range 48.6-63.6 ml) and decreases in maximum detrusor pressure during the storage phase (50 U, -12.9; 100 U, -20.1; 200 U, -27.3 cmH_2O; p = 0.0157, 200 U vs. 50 U). The proportion of patients experiencing involuntary detrusor contractions dropped from baseline (50 U, 94.4%; 100 U, 88.1%; 200 U, 92.6%) to Week 6 (50 U, 61.8%; 100 U, 44.7%; 200 U, 46.4%). Safety was similar across doses; urinary tract infection was most frequent.

Conclusions: OnabotulinumtoxinA was well tolerated and effective for the treatment of NDO in children; 200 U showed greater efficacy in reducing bladder pressure and increasing bladder capacity.

IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study
Florian Heinen, Petr Kanovský, A Sebastian Schroeder , Henry G Chambers, Edward Dabrowski, Thorin L Geister, Angelika Hanschmann, Francisco J Martinez-Torres, Irena Pulte, Marta Banach, Deborah Gaebler-Spira

Purpose: Investigate the efficacy and safety of multipattern incobotulinumtoxinA injections in children/adolescents with lower-limb cerebral palsy (CP)-related spasticity.
Methods: Phase 3 double-blind study in children/adolescents (Gross Motor Function Classification System - Expanded and Revised I-V) with unilateral or bilateral spastic CP and Ashworth Scale (AS) plantar flexor (PF) scores $\geqslant$ 2 randomized (1:1:2) to incobotulinumtoxinA (4, 12, 16 U/kg, maximum 100, 300, 400 U, respectively) for two 12- to 36-week injection cycles. Two clinical patterns were treated. Pes equinus (bilateral or unilateral) was mandatory; if unilateral, treatment included flexed knee or adducted thigh.
Endpoints: Primary: AS-PF change from baseline to 4 weeks; Coprimary: investigator-rated Global Impression of Change Scale (GICS)-PF at 4 weeks; Secondary: investigator's, patient's, and parent's/caregiver's GICS, Gross Motor Function Measure-66 (GMFM-66).
Results: Among 311 patients, AS-PF and AS scores in all treated clinical patterns improved from baseline to 4-weeks post-injection and cumulatively across injection cycles. GICS-PF and GICS scores confirmed global spasticity improvements. GMFM-66 scores indicated better motor function. No significant differences between doses were evident. Treatment was well-tolerated, with no unexpected treatment-related adverse events or neutralising antibody development.
Conclusion: Children/adolescents with lower-limb spasticity experienced multipattern benefits from incobotulinumtoxinA, which was safe and well-tolerated in doses up to 16 U/kg, maximum 400 U.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 22, 2023
Search Strategy:

#	Searches	Results
1	abobotulinumtoxinA.mp.	495
2	incobotulinumtoxinA.mp.	494
3	onabotulinumtoxinA.mp.	1282
4	prabotulinumtoxinA.mp.	23
5	rimabotulinumtoxinB.mp.	628
6	1 or 2 or 3 or 4 or 5	2531
7	limit 6 to (english language and humans and yr="2018 -Current")	709
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	87

Appendix 4: Key Inclusion Criteria

Population	Patients with indications for botulinum toxin
Intervention	Botulinum toxin A and botulinum toxin B
Comparator	Placebo or active treatment
Outcomes	Dependent upon indication being treated (see Table 2)
Timing	Not applicable
Setting	Outpatient

Botulinum Toxins

Goal(s):
- Approve use of botulinum toxins for conditions funded under the Oregon Health Plan (OHP) and supported by evidence of benefit.
- Require positive response to therapy for continued use to manage chronic migraine headaches or overactive bladder.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- From 90 days to 12 months

Requires PA:
- Use of botulinum toxins (billed as a physician administered or pharmacy claim) without associated dystonia or neurological disease diagnosis in last 12 months.

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor muscle over-activity ("overactive bladder")?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83) b. Strabismus due to a neurological disorder (H50.89) c. Blepharospasm (G24.5) d. Spasmodic torticollis (G24.3) e. Torsion dystonia (G24.9) f. Achalasia (K22.0)	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5 Baseline headaches per month: _____	**No:** Go to #8
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different drug classes)? • Propranolol immediate-release, metoprolol, or atenolol • Topiramate, valproic acid, or divalproex sodium • Amitriptyline, nortriptyline, or venlafaxine	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve no more than 2 injections given ≥3 months apart within a 12 month time period. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).

Approval Criteria		
8. Is botulinum toxin treatment detrusor muscle over-activity ("overactive bladder")?	**Yes:** Go to #9	**No:** Pass to RPh. Go to #10
9. Has the patient had an inadequate response to, or is intolerant to at least ~~of, ≥~~two urinary incontinence antimuscarinic or beta-3 adrenergic therapies~~2~~, such as those listed below ~~of the following drugs~~? a. Fesoterodine (OHP preferred) b. Oxybutynin (OHP preferred) c. Solifenacin (OHP preferred) d. Darifenacin e. Flavoxate f. Mirabegron g. Tolterodine h. Trospium i. Vibegron	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

10. Review treating condition, age, and ICD-10 code. ICD-10 codes included in the tables below are denied. If ICD-10 code is not included in the tables below, medical literature with evidence for use in funded conditions must be submitted by the prescriber. RPh may approve for up to 12 months for funded conditions with evidence of benefit.

If current age ≥21 years: Deny for the following conditions; not funded by the OHP **If current age <21 years, evaluate FDA-approved indications and disease severity. If the drug is FDA approved for the condition AND prescriber submits documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)~~that disease impacts health or quality of life~~, RPh may approve for up to 12 months.**
▪ Axillary hyperhidrosis and palmar hyperhidrosis (L74.52, R61) ▪ Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259) ▪ Facial nerve disorders (G510-G519) ▪ Spastic dysphonia (J387) ▪ Anal fissure (K602) ▪ Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61) ▪ Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788) ▪ Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549) ▪ Disorders of soft tissue (M5410; M609; M790-M792; M797) ▪ Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51) ▪ Gastroparesis (K3184) ▪ Lateral epicondylitis (tennis elbow)~~)~~ (M7710-M7712) ▪ Unspecified diseases of the salivary glands (sialorrhea) (K11.5-K11.9,R68.2)
Deny for medical appropriateness because evidence of benefit is insufficient

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

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

P&T / DUR Review: *6/23 (KS),4/22 (AG); 5/19 (KS); 9/18; 5/18; 11/15; 9/14; 7/14*
Implementation: *TBD; 5/1/22; 11/1/2018; 7/1/18; 10/13/16; 1/1/16*

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Drug Class Update with New Drug Evaluation: *Clostridioides difficile* Drugs

Date of Review: June 2023

Date of Last Review: May 2018
Dates of Literature Search: 03/14/2018 – 02/07/2023
Brand Name (Manufacturer): Rebyota (Ferring Pharmaceuticals)
Dossier Received: yes

Generic Name: fecal microbiota, live-jslm

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

Purpose for Class Update:
To review a new Food and Drug Administration (FDA)-approved biotherapeutic, fecal microbiota live-jslm (REBYOTA), indicated for the prevention of recurrent *Clostridioides (*formerly *Clostridium) difficile* infection (CDI) in adults. In addition, any new comparative evidence for existing agents approved to treat CDI or prevent CDI recurrence will be reviewed and summarized.

Plain Language Summary:
- This review looks at new evidence for medicines used to manage infections in the large intestine (colon) caused by a bacterium called *Clostridioides difficile* (also called *C. difficile*). Illness from *C. difficile* can occur after the use of antibiotic medicines to treat another infection elsewhere in the body. Many antibiotics destroy the healthy bacteria that normally live in the large intestine. This allows *C. difficile* to take over and release toxins that can damage the large intestine. Symptoms of this infection include frequent episodes of watery diarrhea, nausea, and stomach cramps. *C. difficile* can be difficult to treat because it may come back within 8 weeks after a finishing antibiotic therapy, also known as *C. difficile* recurrence.
- Currently, providers can prescribe 2 antibiotics to treat infections caused by *C. difficile.* These antibiotics are fidaxomicin and vancomycin. Studies show these antibiotics improve diarrhea caused by *C. difficile* and prevent recurrence of infection. These 2 medicines have similar side effects. Multiple organizations including the Infectious Diseases Society of America and American College of Gastroenterology recommend one of 2 these medicines to treat the first onset of a *C. difficile* infection and to prevent recurrent *C. difficile* infections.
- The Food and Drug Administration has also approved another medicine, called bezlotoxumab, to prevent *C. difficile* infections from coming back. This medicine is an infusion administered in the veins by a health care provider. It is not used to treat *C. difficile* infection, only to prevent recurrence of infection.
- Since 2013, the Food and Drug Administration has authorized use of stool transplants, or fecal microbiota transplantation, where providers administer donor stool to a person with *C. difficile* infection. This process replaces the good bacteria that help maintain healthy large intestine activity and helps prevent *C. difficile* infection from recurring.
- The Food and Drug Administration recently approved a commercial formulation of fecal microbiota suspension (REBYOTA) which is used to prevent recurrent infections caused by *C. difficile*. This medicine is administered as an enema and contains human stool microbiota from healthy donors.

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- The British Society of Gastroenterology and Healthcare Infection Society suggest providers offer fecal microbiota transplantation to people who have experienced at least 2 recurrences of *C. difficile* infection. The American College of Gastroenterology and National Institute for Health and Care Excellence also support this recommendation to prevent additional recurrences.
- The Oregon Health plan covers vancomycin capsules. Providers must explain to the Oregon Health Authority why someone needs fidaxomicin, vancomycin suspension, or bezlotoxumab before Medicaid will pay for it. This process is called prior authorization.
- We recommend updates to policies for fidaxomicin and bezlotoxumab to align with current evidence. We recommend that the Oregon Health plan only pay for fecal transplant when other therapies have not cured *C. difficile* infection after 2 recurrences.

Research Questions:

1. What is the comparative efficacy or effectiveness of metronidazole, vancomycin and fidaxomicin for treatment of an initial CDI or recurrent CDI?
2. What are the comparative harms of metronidazole, vancomycin and fidaxomicin when used for treatment of an initial CDI or recurrent CDI?
3. Is there new evidence or guidance for the use of bezlotoxumab for preventing recurrent CDI?
4. What is the evidence for the safety and efficacy of fecal microbiota live-jslm (REBYOTA) in preventing recurrent CDI?
5. Are there specific subpopulations of patients (specifically by race, age, socio-economic status, or comorbidities) for which one therapy is more effective or associated with more harm than other therapies when used to manage CDI or recurrence?

Conclusions:

- Since the Drug Use Research Management (DURM) 2018 class update of CDI treatment, 2 systematic reviews[1,2] and 5 guidelines[3-7] have been published to evaluate the use of fidaxomicin, metronidazole, or vancomycin in treating initial and recurrent CDI and the use of bezlotoxumab or fecal microbiota transplant to prevent recurrent CDI.

Treatment of Initial or Recurrent CDI with Vancomycin or Fidaxomicin and Prevention of Recurrent CDI with Bezlotoxumab

- A 2022 systematic review and meta-analysis evaluated the safety and efficacy of oral fidaxomicin versus oral vancomycin in a mixed population of patients with an initial CDI episode and patients with recurrent CDI.[1] The primary endpoint was global cure for efficacy, calculated as the ratio of the number of patients who did not experience CDI recurrence after achievement of clinical cure (resolution of diarrhea and no need for further CDI treatment) with the total number of patients enrolled in the studies.[1] Compared to vancomycin, moderate quality evidence showed fidaxomicin was associated with higher global cure rates (risk ratio [RR]=1.18, 95% confidence interval [CI]=1.09 to 1.26; p<0.00001).[1] Clinical cure rates were calculated as the ratio of the number of patients with resolution of diarrhea following the end of treatment to the total number of patients enrolled in the studies.[1] Clinical cure rates were similar between fidaxomicin and vancomycin (RR=1.02, 95% CI=0.98 to 1.06, p=0.31; moderate quality evidence).[1] Fidaxomicin was associated with lower CDI recurrence rates than vancomycin (RR=0.59, 95% CI=0.47 to 0.75, p<0.0001; moderate quality evidence).[1] Adverse event rates were not different between the 2 antibiotics (P=0.41).[1]
- For initial treatment of CDI, 2021 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recommend oral fidaxomicin 200 mg given twice daily for 10 days as first line treatment (conditional recommendation, moderate certainty of evidence).[4] Oral vancomycin 125 mg taken 4 times daily for 10 days is a reasonable alternative.[4] If patients have non-severe CDI symptoms or if fidaxomicin or vancomycin are unavailable, oral metronidazole 500 mg taken 3 times a day for 10 to 14 days is a treatment of last resort.[4] Fidaxomicin and vancomycin are considered standard-of-care (SOC) antibiotics for initial management of CDI.[4] These recommendations are supported by 2021 American College of Gastroenterology guidance.[5]
- National Institute for Health and Care Excellence (NICE) guidance for initial CDI antibiotic treatment was published in 2021,[6] and differs slightly from IDSA/SHEA and ACG recommendations. For treatment of an initial episode of CDI, NICE recommends oral vancomycin as the first-line antibiotic of choice.[6]

Fidaxomicin is recommended as the second-line antibiotic for a first episode of C. difficile infection of any severity when vancomycin is ineffective (i.e., treatment failure).[6] Although fidaxomicin was more effective than vancomycin for sustained symptomatic cure in an indirect network meta-analysis, the cost of fidaxomicin is substantially higher than vancomycin in the United Kingdom.[6] Metronidazole is not recommended for treating an initial CDI episode per NICE guidance.[6]

- A 2020 systematic review assessed safety and efficacy of interventions to prevent recurrent CDI.[2] Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.[4] For prevention of recurrent CDI, there is at least one study to support fidaxomicin (compared to a 10-day vancomycin course; low-quality evidence), fecal microbiota transplant (FMT) (compared to a 14 day vancomycin regimen; moderate quality evidence), and bezlotoxumab (compared to placebo; moderate-quality evidence).[2] While the results of 3 low-quality RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.[2]
- The 2021 IDSA/SHEA updated guidance focused on recently published evidence for the use of fidaxomicin in treating recurrent CDI compared with vancomycin and the use of bezlotoxumab as monotherapy or in conjunction with standard-of-care antibiotics (SOC) in preventing recurrent CDI.[4] In patients with recurrent CDI episodes, IDSA/SHEA guidance suggests fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty of evidence).[4] For patients with a recurrent CDI episode within the last 6 months, guidance suggests bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, very low certainty of evidence).[4] The 2021 ACG guidelines for treating recurrent CDI are similar to IDSA/SHEA, including a statement that there is insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI.[5] For recurrent CDI which develops more than 12 weeks after symptom resolution, either vancomycin or fidaxomicin is recommended by 2021 NICE guidance.[6]

Fecal Microbiota Transplant for Prevention of Recurrent CDI

- A 2018 joint guideline developed by the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) provided recommendations for best practices for the provision of fecal microbiota transplant (FMT) in adults with CDI before commercial products were available.[3] Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:
    - FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).[3]
    - FMT should be offered to patients with recurrent CDI who have had at least 2 recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong recommendation, high-quality evidence).[3]
    - FMT should be considered in cases of severe CDI (strong recommendation, moderate-quality evidence).[3]
- The ACG 2021 guidance includes a recommendation that patients experiencing their second or more recurrence of CDI be treated with FMT to prevent additional recurrences (strong recommendation, moderate-quality evidence).[5] This recommendation is supported by 2022 NICE guidance.[7]

Safety and Efficacy of Fecal Microbiota Suspension (REBYOTA)

- Fecal microbiota (REBYOTA) is a live biotherapeutic suspension for rectal administration FDA-approved for prevention of recurrent CDI in adults aged 18 years and older following SOC antibiotic treatment for recurrent CDI.[8] Approval was based on findings from a placebo-controlled phase 3 RCT (PUNCH CD3) and a phase 2 RCT (PUNCH CD2).[9] In a pooled analysis of both trials, low-quality evidence shows the overall estimated rate of success in preventing recurrent CDI was higher in the fecal microbiota group (70.6%) than in the placebo group (57.5%) 8 weeks after transplantation.[9] The most commonly reported adverse events reported after a single dose of fecal microbiota suspension included abdominal pain (9%), diarrhea (7%), abdominal distention (4%), flatulence (3%) and nausea (3%).[8] Safety and efficacy of REBYOTA in people younger than 18 years of age have not been established.[8] There is insufficient evidence to assess comparative safety and efficacy of REBYOTA with compounded FMT products.

Expanded Indications for Antibiotics in the C. difficile PDL Class

- A new oral suspension formulation of vancomycin (FIRVANQ) was approved in January 2018.[10] This product is indicated in adults and pediatric patients less than 18 years of age (no lower age limit is stated in the prescribing information) for treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus*.[10]
- In January 2020, the FDA expanded the approved population eligible to receive fidaxomicin (DIFICID) to include pediatric patients aged 6 months and older.[11]

Specific Populations at Higher Risk for Adverse Effects with FMT

- The 2018 BSG/HIS guidance identified several groups of patients who may experience more harm from non-commercial FMT products based on low to moderate quality evidence which includes: patients with significant/anaphylactic food allergy, other infectious cause of diarrhea, inflammatory bowel disease, immunodeficiency due to recent chemotherapy and/or neutropenia, human immunodeficiency virus, prolonged use of corticosteroids, and decompensated cirrhosis.[3] REBYOTA is manufactured from human fecal matter and may contain food allergens. However, the potential for REBYOTA to cause adverse effects due to food allergens is currently unknown.[8]

Recommendations:

- Maintain fidaxomicin as a non-preferred drug on the Practitioner-Managed Prescription Drug Plan (PMPDP). Retire current prior authorization (PA) criteria and rely on non-preferred PA criteria to verify FDA-approved indication for *C. difficile* prior to fidaxomicin approval.
- Designate fecal microbiota (REBYOTA) as a non-preferred drug on the PMPDP subject to PA. Create a new set of PA criteria titled "Prevention of *C. difficile* Recurrence" and include bezlotoxumab infusion and fecal microbiota enema in the new document.
- Retire current bezlotoxumab PA criteria.
- Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

- Medications FDA-approved to treat CDI were last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the May 2018 meeting. The evidence for the safety and efficacy for a new monoclonal antibody, bezlotoxumab (ZINPLAVA), was presented. Bezlotoxumab is indicated for reducing the incidence of recurrent CDI in combination with SOC antibiotic therapy in adults at high risk for CDI recurrence.[12] Guideline updates published by IDSA/SHEA in 2017 recommend using oral vancomycin or fidaxomicin for an initial CDI episode.[13] Metronidazole is no longer recommended as a first line agent, except in circumstances where access to vancomycin or fidaxomicin is limited or in initial cases of non-severe CDI.[13] The recommendations for treating recurrent CDI suggest trying an alternative antibiotic (vancomycin or fidaxomicin) than the medication that was used for the first episode of CDI.[13] Metronidazole is not recommended for treatment of recurrent CDI.[13] Although the comparative effectiveness of metronidazole and vancomycin in pediatric CDI is insufficient, either weight-based oral metronidazole or vancomycin are recommended for an initial episode or first recurrence of CDI in children.[13] At that time, fidaxomicin was not FDA-approved for use in children less than 18 years of age, so it was not included in the 2017 IDSA/SHEA pediatric recommendations.[13]
- After reviewing the evidence, the P & T committee accepted the recommendation to designate bezlotoxumab as non-preferred drug on the PMPDP subject to PA. Fidaxomicin PA criteria were modified to remove metronidazole as a prerequisite to fidaxomicin in patients with recurrent CDI.
- The preferred drug list status for medications used to treat CDI or prevent recurrent CDI is summarized in **Appendix 1**. Vancomycin capsules and metronidazole tablets are preferred agents on the preferred drug list (PDL). Fidaxomicin, vancomycin oral suspension, and bezlotoxumab are non-preferred agents and require PA. The PA criteria for bezlotoxumab and fidaxomicin are presented in **Appendix 6**.
- In the third quarter of 2022, all claims for agents in the *C. difficile* class were for metronidazole tablets and preferred formulations of vancomycin. In the first 3 quarters of 2022, there were no physician administered claims for bezlotoxumab in the Fee-for-Service population.

Background:

The bacterial genus *Clostridium* was reclassified as *Clostridioides* in 2016.[14] C*lostridioides difficile,* a spore-forming, gram-positive, anaerobic bacillus, is the primary pathogen of infectious diarrhea in hospitalized patients.[15] The bacteria produces 2 exotoxins, toxin A and toxin B, which disrupt colonic epithelial integrity, stimulate release of inflammatory mediators, and result in pseduomembrane formation.[16] Any surface or device (such as commodes, bathtubs, and electronic rectal thermometers) that becomes contaminated with feces could serve as a reservoir for the *C. difficile* spores.[15] The spores can also be transferred to patients via the hands of healthcare personnel who have touched a contaminated item.[15] The Centers for Disease Control and Prevention (CDC) has identified CDI as an urgent global public health threat due to the emerging prevalence of more virulent *C. difficile* strains and increasing mortality rates due to resistant strains of the bacteria.[17] According to a 2019 CDC report, an estimated 223,900 cases in hospitalized patients and 12,800 deaths in the United States were associated with CDI.[17] High CDI recurrence rates after appropriate treatment (30 to 65%) is a public health challenge.[18] Community associated CDI is on the rise and is estimated to occur in one third of all CDI cases.[19] *C.difficile* infection can result in pseudomembranous colitis, toxic megacolon, colon perforations, sepsis, and mortality.[15]

Broad spectrum antibiotic exposure, in particular clindamycin, carbapenems, cephalosporins and fluoroquinolones, increases the risk of developing CDI.[20] These antibiotics disrupt normal gut flora which results in *C. difficile* overgrowth in the colon. Other risk factors for CDI include: age greater than 65 years; long length of stay in healthcare settings; gastrointestinal surgical procedures; immunocompromising conditions; inflammatory bowel disease; or a serious underlying illness.[15] To reduce the risk of CDI, the frequency, number of agents prescribed, and duration of high-risk antibiotic therapy should be minimized.[21] In addition to antibiotic stewardship, strategies to reduce CDI include policies focused on effective infection control (e.g., contact isolation procedures, hand hygiene practices before and after patient contact) and healthcare facility cleaning and disinfection.[17]

The diagnosis of CDI is based on clinical history and laboratory findings of *C. difficile* toxins in the stool. Symptoms include presence of diarrhea (defined as 3 or more unformed stools in 24 hours), cramps, fever, loss of appetite, nausea and lower abdominal pain.[15] Laboratory testing cannot distinguish between colonization and infection. The gold standard for CDI diagnosis is lab verification of toxigenic *C. difficile* in stool along with histopathology showing psuedomembranes in patients with clinical symptoms.[16] Treatment goals include resolution of diarrhea and reduction of CDI recurrence. Severe CDI may be accompanied by leukocytosis with a white blood cell count (WBC) greater than 15,000 cells/µL and elevated serum creatinine 1.5 times the patients' baseline value secondary to dehydration from extensive diarrhea. Some of the literature uses a Zar score to stratify patients with CDI into mild or severe groups. In the Zar severity scoring, one point each is assigned for age greater than 60 years, temperature greater than 38.3°C, albumin level less than 2.5 mg/dL, and WBC greater than 15,000 cells/µL.[22] Patients that score greater than or equal to 2 points are considered to have severe CDI.[22] Severe, complicated CDI can result in shock, hypotension, ileus, or megacolon.

Treatment of CDI is based on risk of recurrence and severity of symptoms. For an initial episode of CDI, IDSA/SHEA (2017) recommends either vancomycin 125 mg orally four times a day or fidaxomicin 200 mg twice daily for 10 days.[21] Metronidazole is no longer recommended as first-line therapy for CDI in adults and is only indicated if allergy or intolerance limit prescribing vancomycin or fidaxomicin. Recurrent CDI is defined by IDSA/SHEA as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.[21] For the first recurrence of CDI, a prolonged tapered and pulsed vancomycin regimen (standard vancomycin course for 10-14 days followed by decreasing the dose by 25%-50% every 1-2 weeks with no skipped days and then pulsed at a 125-mg dose, skipping 1 to 2 days, for 2-4 weeks) or a 10-day course of fidaxomicin is recommended if vancomycin was used for the initial episode.[21] For recurrent CDI, IDSA/SHEA (2017) recommends 10 days of vancomycin followed by 20 days of rifaximin or fidaxomicin.[21] For non-severe CDI in children, either weight-based metronidazole or vancomycin dosing is recommended for an initial episode or first CDI recurrence.[21] For severe CDI in children, oral vancomycin is recommended over metronidazole by IDA/SHEA (2017).[21]

Bezlotoxumab, an anti-toxin B monoclonal antibody, was FDA approved in 2016 for prevention of CDI recurrence in combination with CDI SOC antibiotics. Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg intravenous (IV) infusion.[12] The evidence for the safety and efficacy of bezlotoxumab was reviewed by the P and T Committee at the May 2018 meeting.

Probiotics are live, generally nonpathogenic bacteria capable of colonizing the colonic mucosa, and have been studied in the prevention of recurrent CDI because of their potential to restore the intestinal microflora.[2] Prebiotics are dietary components that foster the growth of beneficial bacteria, and therefore may serve a similar function as probiotics on the prevention of recurrent CDI.[2] None of these therapies are currently recommended for prevention of CDI in the IDSA (2017) guidelines.[21]

If there are 2 or more CDI recurrences despite appropriate antibiotic treatments, FMT is recommended by IDSA/SHEA (2017).[21] Transplantation occurs by instillation of processed stool donated by a healthy volunteer via nasogastric/nasoduodenal tube, colonoscopy, enema, or capsule.[23] An important barrier to the integration of FMT into regular clinical practice is the heterogeneity of administration routes and lack of standardization of FMT guidance.[23] Standardization of the methodological components of FMT includes: donor screening, stool preparation, storage, and instillation route.[23] In 2017, a FMT national registry including 20 North American practice sites was established by the AGA.[24] The purpose of the registry is to collect data on the efficacy of FMT on the cure of CDI within 6 months after treatment, and to evaluate short-term and long-term safety of FMT. As of 2021, 259 participants were enrolled in the program.[24] At 1-month follow-up, 90% of participants (n=222) had experienced cure of CDI and only required one treatment with FMT to achieve cure.[24] Of the participants who had a 6-month follow-up (n=145), 88% reported a CDI cure.[24] Post-FMT adverse effects occurred in 45% of participants (n=106).[24] The most commonly reported adverse effects at 1 month included non-CDI diarrhea (30%), abdominal pain (17%), bloating (15%), and constipation (10%).[24] New infections possibly related to FMT occurred in 2 participants (1%) and hospitalizations possible related to FMT occurred in 3 participants (1%) up to 1 month after transplantation.[24] Serious adverse events reported to the registry between 1 and 6 months after FMT included infections (4%) and hospitalizations (19%).[24]

In June 2019, the FDA released a statement warning of the risks associated with FMT due to transmission of multi-drug resistant organisms.[25] Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E. Coli)*; of the 2 adults, one of the individuals died.[25] Another warning was issued March 2020, reporting 6 additional cases of transmission of antibiotic-resistant organisms (enteropathogenic *E. coli* in 2 cases and Shigatoxin-producing *E. coli* in 4 cases) via FMT.[26] In April 2020, the FDA issued a safety alert requiring testing of stool donors for SARS-CoV-2 virus due to possible risk of viral transmission from donor to recipient.[27] In August 2022, a similar safety alert regarding possible transmission of monkeypox virus via FMT was published to recommend additional donor screening parameters.[28]

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

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

Systematic Reviews:

Oral Fidaxomicin Versus Oral Vancomycin for Treatment of *C. Difficil*e Infection

A 2022 systematic review and meta-analysis evaluated the safety and efficacy of oral fidaxomicin versus oral vancomycin in patients with CDI.[1] Literature was searched through October 2021 and 6 RCTs (n=682) met inclusion criteria.[1] Five studies were conducted in Western countries (America, Canada, or Europe), and one study was conducted in Japan.[1] The studies included a mixed population of patients with an initial CDI episode and patients with recurrent CDI. Three RCTs provided CDI severity data and reported the percentage of patients with severe CDI ranged from 22.2% to 39.4%.[1] The primary endpoint was global cure for efficacy and secondary endpoints included clinical cure, recurrence, and adverse events.[1] Two of the RCTs were open-label clinical trials and had high risk of performance and detection bias.[1] The other 4 RCTs had low risk of bias and were conducted without industry support.[1]

The primary endpoint, global cure for efficacy, was calculated as the ratio of the number of patients who did not experience CDI recurrence after achievement of clinical cure (resolution of diarrhea and no need for further CDI treatment) with the total number of patients.[1] Compared to vancomycin, moderate quality evidence showed fidaxomicin was associated with higher global cure rates (RR=1.18, RD=0.11, 95% CI=1.09 to 1.26; p<0.00001).[1] Fidaxomicin was also associated with lower recurrence rates than vancomycin (RR=0.59, 95% CI=0.47 to 0.75, p<0.0001; moderate quality evidence).[1] Clinical cure rates were calculated as the ratio of the number of patients with resolution of diarrhea (during treatment and at the end of treatment) and no further need for treatment of CDI with the total number of patients.[1] Clinical cure rates were comparable between fidaxomicin and vancomycin (RR=1.02, 95% CI=0.98 to 1.06, p=0.31; moderate quality evidence).[1] Adverse event rates were not different between the 2 antibiotics (P=0.41).[1]

Most of the studies were conducted in the United States, Canada, and Europe. Regional resistance patterns may impact these results, and it is unclear if other clinical locations would have similar outcomes.[1] In addition, this systematic review was limited by heterogeneous trial populations and outcome measures, with different time points for efficacy evaluation and follow-up periods (38 to 60 days), and mixed populations of patients with CDI (initial episode versus recurrent episodes).[1]

Prevention of Recurrent *C. Difficile* Infection

A 2020 systematic review assessed safety and efficacy of interventions to prevent recurrent CDI.[2] The literature search for eligible RCTs was conducted through February 2018. Thirty-eight RCTs (n=8,102) met inclusion criteria.[2] Of the 38 studies, 19 assessed antibiotics (n=3,743); 8 assessed FMT (n=582); 3 assessed monoclonal antibodies (n=2,805); and 8 assessed prebiotics, probiotics, and non-antibiotic polymers (n=972).[2] Studies were included irrespective of patient demographics, disease severity, type of intervention, comparator used, or time-point of outcome evaluation.[2] Overall, the majority of studies included adult participants aged 55 years and older.[2] There were two exceptions: one FMT study included patients as young as 7 years of age, resulting in the enrollment of 3 children, and another FMT study excluded patients 75 years and older.[2] All studies required participants to have at least one episode of CDI at the time of enrollment. However, the number of prior CDI episodes accepted at inclusion was not uniform across the trials.[2] Five studies evaluating FMT and 6 trials assessing antibiotics were open-label trials with high risk of performance and detection bias.[2] Four studies had a high risk of attrition bias.[2] Six trials were pilot studies and were likely underpowered.[2] The study methodology was not clear in 4 trials.[2] There was low of risk of bias for 14 of the 38 included RCTs.[2]
Four studies compared fidaxomicin to vancomycin in patients with recurrent CDI.[2] One study was a small pilot (n=12) and was underpowered to detect differences between therapies. Two trials were non-inferiority RCTs, and one trial was an open-label Phase 3b/4 trial. Low-quality evidence from these trials found a reduction in recurrent CDI in the fidaxomicin treatment group compared with vancomycin (RR 0.39, 95% CI 0.24 to 0.65; RR 0.10, 95% CI 0.03 to 033; RR

0.54, 95% CI 0.35 to 0.84).[2] The adverse effects associated with fidaxomicin included electrolyte imbalances, laboratory abnormalities, pruritus, bile stone formation, and drug hypersensitivity.[2] Adverse effects observed with vancomycin were not reported in the systematic review.
Of the 8 FMT studies, 3 moderate-quality RCTs (n=110 participants) compared the efficacy of FMT to vancomycin therapy. The first study (n=39) found that FMT was more effective in preventing recurrent CDI compared to a ten-day course plus three-week taper of oral vancomycin (RR 0.47, 95% CI 0.25 to 0.91).[2] A second study (n=43) demonstrated FMT was more effective in preventing recurrent CDI than a 14-day vancomycin course (RR 0.27, 95% CI 0.09 to 0.80) and a 14-day vancomycin course plus bowel lavage (RR 0.24, 95% CI 0.08 to 0.71).[2] A third study (n=28) included a vancomycin taper regimen of 6 weeks, but was stopped for futility at the interim analysis (RR 1.35, 95% CI, 0.61 to 2.99).[2] In 2 of the 3 trials, moderate-quality evidence showed that FMT appeared to be superior to treatment with oral vancomycin in the prevention of recurrent CDI.[2] The other 5 studies (n=473) compared different preparations and routes of administration of FMT including: frozen FMT administered by colonoscopy compared with fresh FMT and lyophilized microbiota, frozen FMT compared to fresh FMT administered via enema, FMT capsules compared with colonoscopic infusion, and nasogastric tube versus colonoscopic administration of FMT.[2] Overall, there were no significant differences in outcomes for the different routes or preparations of FMT.[2] All of the studies evaluating FMT reported adverse events including bloating, abdominal cramping and distension, nausea, and vomiting.[2] No trials reported serious adverse events that were considered to be related to FMT.[2]

Two moderate-quality phase 3 trials (MODIFY I and MODIFY II) were conducted to evaluate the safety and efficacy of bezlotoxumab, a monoclonal antibody, in reducing the incidence of recurrent CDI.[29] In both MODIFY I and MODIFY II, the rate of CDI recurrence through week 12 was significantly lower in the bezlotoxumab arms compared to the placebo arms (MODIFY I: 17% vs. 28%; 95% CI, -15.9 to -4.3; p <0.001; MODIFY II: 16% vs 26%; 95% CI -15.5 to -4.3; p < 0.001).[29] Bezlotoxumab is not indicated for the treatment of CDI and is only approved for use in combination with SOC antibiotics in adults at high risk for CDI recurrence as a single 10 mg/kg infusion.[30] In these 2 RCTs, there were infusion-related adverse events and serious adverse events related to bezlotuoxumab.[2] Five patients who received bezlotoxumab alone experienced diarrhea, ventricular tachyarrhythmia, hematuria, cerebral hemorrhage, and sepsis.[2] The patient who had cerebral hemorrhage and sepsis died as a result of their complications.[2]

Compared to placebo, prebiotics or probiotics were more effective for prevention of recurrent CDI in 3 RCTs. These low-quality RCTs evaluated the prebiotic, oligofructose (RR 0.24, 95% CI, 0.11 to 0.56), the probiotic, S. boulardii (RR 0.59, 95% CI, 0.35 to 0.98), and 7-day course of nontoxigenic C. difficile strain M3 (RR 0.11, 95% CI, 0.02 to 0.54).[2] While the results of 3 RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.[2] The other 5 probiotic studies did not demonstrate proven benefit in preventing recurrent CDI with these agents.[2] No RCTs evaluating probiotics, prebiotics, or non-antibiotic polymers reported serious adverse events related to the study intervention.[2]

In summary, for prevention of recurrent CDI, there is at least one study to support fidaxomicin (compared to a 10-day vancomycin course; low-quality evidence), fecal microbiota transplant (FMT) (compared to a 14 day vancomycin regimen; moderate quality evidence), and bezlotoxumab (compared to placebo; moderate-quality evidence).[2] While the results of 3 low-quality RCTs using probiotics or prebiotics found benefit in preventing recurrent CDI, the studies were underpowered and further research with larger samples sizes is needed to draw definitive conclusions regarding their efficacy in CDI.[2]

After review, 24 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[31-39] wrong study design of included trials (e.g., observational),[40-53] comparator (e.g., no control or placebo-controlled),[54] or outcome studied (e.g., non-clinical).[55]

New Guidelines:

High-Quality

Infectious Diseases Society of America/Society for Healthcare Epidemiology of America: Focused Update *on C. difficile* Infections

In 2021, the IDSA and SHEA revised guidance on management of CDI in adults.[4] Updates were focused on recently published evidence for the use of fidaxomicin in initial and recurrent CDI compared with vancomycin and the use of bezlotoxumab as monotherapy or in conjunction with SOC antibiotics in preventing recurrent CDI. The guideline committee concluded fidaxomicin and bezlotoxumab may have increased clinical efficacy over older agents, but implementation may be challenging because of initial monetary cost and administration logistics.[4] **Table 1** summarizes 2017 IDSA/SHEA recommendations combined with 2021 IDSA/SHEA focused guidance for the treatment of CDI in adults. No changes were made to the 2017 pediatric guidance.

Three new recommendations were published by the guideline development panel:

1. *For patients with an initial CDI episode, it is suggested to use fidaxomicin rather than a standard course of vancomycin (preferred treatment, conditional recommendation, moderate certainty of evidence).*[4]
   Comment**:** This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources.[4] Additional, well-designed, independent, cost-effectiveness studies for patients with CDI are needed to improve the strength of this recommendation given that cost is a substantial barrier to fidaxomicin use.[4] Vancomycin remains an acceptable alternative.[4]

2. *In patients with recurrent CDI episodes, it is suggested to use fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (preferred treatment, conditional recommendation, low certainty of evidence).*[4]
   Comment: More well-designed RCTs for patients with recurrent CDI, particularly multiple recurrent CDIs, are needed to improve the strength of recommendations.[4] Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence.[4] For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and FMT are options in addition to fidaxomicin.[4]

3. *For patients with a recurrent CDI episode within the last 6 months, it is suggested to use bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (alternative treatment) (conditional recommendation, very low certainty of evidence).*[4]
   Comment: This recommendation places a high value on potential clinical benefits, but implementation is often limited by feasibility considerations.[4] In settings where administration logistics are not an issue, patients with a primary CDI episode and other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host [per history or use of immunosuppressive therapy], and severe CDI on presentation) may particularly benefit from receiving bezlotoxumab.[4] Data on the use of bezlotoxumab when fidaxomicin is used as the SOC antibiotic are limited.[4]

Table 1. IDSA/SHEA Recommendations for Treatment of *Clostridioides difficile* infections in adults[4]

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative to fidaxomicin
	Alternative for non-severe CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of non-severe CDI is supported by the following laboratory parameters: White blood cell count of 15,000 cells/µL or lower and a serum creatinine level <1.5 mg/dL
	Preferred: Fidaxomicin 200 mg given twice daily for 10 days.	

First CDI recurrence	Off-label recommendation: Fidaxomicin 200 mg twice daily for 5 days followed by once every other day for 20 days.	
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics [a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure. [b]
Second or subsequent CDI recurrence	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	
	Vancomycin by mouth in a tapered and pulsed regimen	
	Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days	
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics [a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure. [a]
Fulminant CDI	Vancomycin 500 mg 4 times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

[a] *Bezlotoxumab may also be considered for patients with other risks for CDI recurrence but implementation depends upon available resources and logistics for intravenous administration, particularly for those with an initial CDI episode. Additional risk factors for CDI recurrence include age >65 years, immunocompromised host (per history or use of immunosuppressive therapy), and severe CDI on presentation.*

[b] *The Food and Drug Administration warns that "in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk."*

Abbreviations: CDI = *Clostridioides difficile* infection; IDSA/SHEA = Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; SOC = standard of care

The guideline panel identified areas where additional research is needed. These areas included:

- Evaluation of total costs with fidaxomicin (e.g., with reduced CDI recurrences and greater initial acquisition cost);
- Comparison of standard and extended-dosing fidaxomicin versus extended-dosing of vancomycin;

- Evaluation of fidaxomicin for treatment of fulminant CDI;
- Direct comparisons of narrow-spectrum antibiotics for prevention of recurrence;
- Evaluation of biotherapeutics or FMT to restore the microbiome; and
- Evaluation of bezlotoxumab (or similar agents) alone or in combination with other antibiotics (e.g., in combination with fidaxomicin) to augment the host immune response.[4]

American College of Gastroenterology: Treatment of *C. difficile* Infection

In 2021, the ACG updated 2013 recommendations on the prevention, diagnosis, and treatment of CDI.[5] This publication was intended to complement the IDSA/SHEA 2021 updates.[5] THE ACG panel chose to expand on areas of particular interest to gastroenterologists, including diagnostic issues around diarrhea and distinguishing *C. difficile* colonization from active infection, the evaluation and management of CDI in the setting of inflammatory bowel disease, and the current evidence and best practices around FMT.[5] This class update focuses on recommendations for medical treatment of CDI.

Antibiotics For Treatment of Initial CDI Episode

The previous ACG Practice Guideline (2013) recommended oral metronidazole for mild-to-moderate CDI and vancomycin for severe CDI.[56] Fidaxomicin was mentioned, but not yet recommended because of increased cost and evolving data. Recent data supports the efficacy of vancomycin and fidaxomicin as primary treatment in nonsevere CDI.[5] Fidaxomicin has been demonstrated to be generally equivalent to vancomycin in this population for cure, with data demonstrating decreased CDI recurrence rates.[5] For lower-risk patients (i.e., younger outpatients with minimal comorbidities), particularly in cost-sensitive environments, metronidazole is an appropriate alternative.[5]

In patients with severe disease, fidaxomicin was noninferior to vancomycin in achieving clinical cure at the end of therapy and associated with decreased risk of recurrence in one phase 3 clinical trial.[5] This and other clinical trials of fidaxomicin have excluded patients with fulminant CDI and life-threatening illness, therefore limited evidence supports fidaxomicin use in these populations.[5] Metronidazole should not be used for the treatment of severe CDI because it was shown to be inferior to vancomycin in multiple RCTs and cohort studies.[5]

In cases of fulminant CDI, a higher dose of oral vancomycin at 500 mg every 6 hours is recommended by IDSA/SHEA (2017)[21] and ACG (2013).[56] Given lack of clinical trial data, this recommendation is based on expert opinion.[5] Direct comparison of low-dose (less than 500 mg/day) and high-dose (greater than 500 mg per day) vancomycin therapies failed to demonstrate significant differences in rates of cure, time to cure, mortality, or complication rates in severe infection.[5] In patients with ileus, the addition of vancomycin enemas (500 mg in 100 mL saline) is also recommended by 2 guidelines[21,56] based on assumptive improvement in colonic drug delivery.[5] Although vancomycin monotherapy is superior to metronidazole in severe CDI, previously published guidelines[21,56] recommend addition of intravenous metronidazole to oral vancomycin in patients with fulminant disease.[5] This recommendation is based on a single-center, retrospective study, where patients with fulminant CDI in the intensive care unit who received vancomycin plus metronidazole had lower rates of mortality compared with vancomycin monotherapy (15.9% vs 36.4%, P=0.03).[5] Although fidaxomicin was shown to be noninferior to vancomycin in the treatment of severe CDI, there are no data supporting its use in fulminant CDI.[5] Strength of recommendations and quality of evidence for initial antibiotic treatment of nonsevere, severe, and fulminant disease are as follows:

- Initial episode of nonsevere disease:
    - Fidaxomicin 200 mg orally twice daily for 10 days (strong recommendation, moderate-quality evidence) or vancomycin 125 mg orally 4 times daily for 10 days (strong recommendation, low-quality evidence).[5]

    - Metronidazole 500 mg orally 3 times daily for 10 days may be considered in patients with low risks (strong recommendation, moderate-quality evidence).[5]
- Severe disease:
    - Vancomycin 125 mg orally 4 times daily for 10 days (strong recommendation, low-quality evidence) or fidaxomicin 200 mg orally twice daily for 10 days (conditional recommendation, very low-quality evidence).[5]
- Fulminant disease:
    - Vancomycin 500 mg orally 4 times daily for the first 48 to 72 hours; if clinical improvement observed, decrease to 125 mg orally 4 times daily for 10 days (strong recommendation, very low-quality evidence).[5]
    - Parenteral metronidazole 500 mg every 8 hours can be considered as an addition to oral vancomycin therapy (conditional recommendation, very low-quality evidence).[5]
    - For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (conditional recommendation, very low-quality evidence).[5]

Treatment of Recurrent CDI

Recurrent CDI is generally defined as the recurrence of diarrhea within 8 weeks after treatment of an initial episode of CDI.[5] Approximately 20% of patients will experience an initial recurrence, and rates of further recurrences continue to increase significantly after each one.[5] Another course of antibiotics is generally required for the treatment of a first recurrence of CDI, and the choice of treatment is dependent on what was used to treat the initial episode.[5] For sustained clinical cure with no recurrence in patients with recurrent CDI, existing data slightly favor fidaxomicin over vancomycin.[5] There are limited data on extended or pulsed vancomycin tapers, and no randomized trials specifically assessing this therapy.[5]

Fecal microbiota transplantation has emerged as a safe and effective therapy for recurrent CDI, which most studies have defined as 3 or more confirmed episodes, although some trials have performed FMT after a second episode.[5] The efficacy of FMT after SOC antibiotics for preventing recurrent CDI has been described in numerous case series and RCTs.[5] There have been a few trials comparing the effectiveness of different FMT delivery modalities.[5] The choice of the most appropriate route of instillation should be driven partly by the options available to the provider, the preferences of the patient, and the clinical circumstances.[5] Minor transient adverse effects associated with FMT have been reported in case series and include bloating, cramps, abdominal pain, nausea, gas, diarrhea, irregular bowel movements, constipation, and low-grade fevers.[5] Serious adverse events have rarely been reported, even among immunocompromised patients, although risk of infection is an important consideration.[5]

Considering the high cost of bezlotoxumab and the minimal benefits over placebo in patients at low risk of recurrent CDI, the ACG panel recommends bezlotoxumab be considered for patients in whom the observed benefits in clinical trials were greatest including those aged 65 years or older with at least one of the following additional risk factors: experiencing a second episode of CDI within the past 6 months, immunocompromised, or severe CDI.[5] Strength of recommendations and quality of evidence for treatment of recurrent CDI are as follows:

- ACG suggests tapering/pulsed-dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low-quality evidence).[5]
- ACG recommends fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (strong recommendation, moderate-quality evidence).[5]
- ACG recommends patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate-quality evidence).[5]

- ACGs recommend FMT be delivered through colonoscopy (strong recommendation, moderate-quality evidence) or capsules (strong recommendation, moderate-quality evidence) for treatment of recurrent CDI; delivery by enema is suggested if other methods are unavailable (conditional recommendation, low-quality evidence).[5]
- ACG suggests repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low-quality evidence).[5]
- ACG suggests bezlotoxumab be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate-quality evidence).[5]

Probiotics

Evidence to evaluate probiotics for preventing CDI is primarily derived from meta-analyses which pooled data from small trials of different probiotic formulations and methodologies.[5] There is a paucity of high-quality clinical trial data of probiotics in CDI, and most studies are underpowered, with CDI as a secondary outcome in studies performed to assess prevention of antibiotic-associated diarrhea.[5] The ACG guideline panel determined that there is insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI.[5] Strength of recommendations and quality of evidence for the use of probiotics are as follows:

- ACG recommends against probiotics for the primary prevention of CDI in patients being treated with antibiotics (conditional recommendation, moderate-quality evidence).[5]
- ACG recommends against probiotics for the secondary prevention of CDI recurrence (strong recommendation, very low-quality evidence).[5]

National Institute for Health and Care Excellence: Antibiotics for *C. difficile* Infection

NICE guidance for CDI antibiotic treatment was published in July 2021.[6] For treatment of an initial episode of CDI, NICE recommends oral vancomycin as the first-line antibiotic for CDI of any severity.[6] Fidaxomicin is recommended as the second-line antibiotic for a first episode of C. difficile infection of any severity when vancomycin is ineffective (treatment failure).[6] Although fidaxomicin was more effective than vancomycin for sustained symptomatic cure in a network meta-analysis, the cost of fidaxomicin is substantially higher in the United Kingdom.[6] Metronidazole is not recommended for treating an initial CDI episode or recurrence of CDI.[6]

For another CDI within 12 weeks of symptom resolution from the first episode (relapse), the NICE committee recommends fidaxomicin.[6] However, if the recurrence develops more than 12 weeks after symptom resolution, either vancomycin or fidaxomicin are recommended.[6] A tapered or pulsed regimen of vancomycin is not recommended because, in the evidence review, its use was limited to studies in which there was co-administration of FMT.[6] The committee agreed that there was insufficient evidence of benefits from a fidaxomicin extended-pulsed regimen to justify recommending an unlicensed treatment regimen over a licensed one in the United Kingdom.[6] If a patient is experiencing a life-threatening CDI, the recommendation is seek specialist advice, with high dose vancomycin (500 mg orally four times a day x 10 days) accompanied by metronidazole 500 mg IV three times a day for 10 days as the suggested antibiotic regimen.[6]

British Society of Gastroenterology and Healthcare Infection Society: Use of Fecal Microbiota Transplant for *C. Difficile* Infection

A joint guideline published by the BSG and HIS in August 2018 provided best practice recommendations for the provision of FMT in adults with CDI based upon the available evidence at that time.[3] If published evidence was insufficient, consensus multidisciplinary expert opinion contributed to recommendation development.[3] The BSG/HIS working group only considered studies that used the administration of manipulated whole stool (including encapsulated feces).[3] Studies using cultured microorganisms (or their proteins, metabolites or other components), or microbiota suspensions, were considered to be in the preclinical

research stage, without firm evidence, and excluded from the evidence analysis.[3] Fifty-eight studies were included as the basis of evidence for writing this guideline.[3] Thirty-nine reports were case studies in CDI including at least 10 patients and 10 were randomized studies in CDI.[3] Nine studies examined FMT efficacy for non-CDI indications (i.e., inflammatory bowel disease, hepatic encephalopathy, metabolic syndrome).[3] For the purposes of this review, the focus will be on guidance for FMT to prevent recurrent CDI.

Candidates for FMT

Evidence for the use of FMT as initial therapy for CDI is very limited, however, there is widespread consensus that FMT is an efficacious treatment for recurrent CDI.[3] In defining recurrent CDI, some studies have relied on a minimum threshold of return of clinical symptoms (e.g., at least 3 unformed bowel movements within 24 hours, for at least 2 consecutive days) following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test.[3] All of the reviewed studies for this guideline included patients with recurrent CDI, but some studies offered FMT to patients at the first recurrence (second episode), whereas others offered FMT after the second recurrence (third episode).[3] Some protocols offered FMT after 3 or more recurrences, while others did not define the point at which FMT was administered.[3] As FMT was an unlicensed medicine in 2018 with poorly-studied long-term sequelae, the working group recommended that it should generally be reserved for patients who have had 3 or more episodes of infection.[3] There were no studies directly comparing its effectiveness with some of the newer agents, such as fidaxomicin or bezlotoxumab, so this recommendation was made on the basis of safety.[3] However, the working group agreed that it may be reasonable in certain patient groups with ongoing risk factors for further CDI recurrence to offer FMT after the second episode.[3]

Two randomized trials assessing FMT efficacy permitted the recruitment of patients with refractory CDI.[3] The first study defined refractory CDI as at least 3 weeks of ongoing severe symptoms despite standard antimicrobial therapy for CDI.[3] The second study required persistent or worsening diarrhea and one of the following: ongoing abdominal pain, fever greater than 38°C, or white blood cell count greater than 15×10^9/L despite oral vancomycin at a dose of 500 mg four times daily for at least 5 days.[3] Both studies included very small numbers of patients with refractory CDI (n=4/20 [20%] and n=15/219 [6.8%], respectively).[3] There did not appear to be any significant difference in primary outcome measure (clinical cure) in patients who received FMT with recurrent or refractory CDI, although neither study was designed to assess this difference.[3] Overall, the working group concluded that there is little consensus on the definition of refractory CDI, with some studies using the terms refractory and recurrent interchangeably.[3] For these reasons, the quality of evidence for the use of FMT in refractory cases of CDI is lower than for recurrent CDI.[3] Strength of recommendations and quality of evidence for which patients are the best candidates for FMT are as follows:

- FMT should not be administered as initial treatment for CDI (strong recommendation, low-quality evidence).[3]
- FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe complicated CDI (strong recommendation, high-quality evidence).[3]
- FMT should be considered in cases of severe, refractory CDI (strong recommendation, moderate-quality evidence).[3]

Comorbidity Exclusions for FMT

Most published studies had a core set of general recipient exclusions which included: significant/anaphylactic food allergy, pregnancy, breastfeeding, admission to intensive care or requirement for vasopressors, chronic diarrhea or other infectious cause of diarrhea, inflammatory bowel disease, immunodeficiency due to recent chemotherapy and/or neutropenia, human immunodeficiency virus, prolonged use of corticosteroids, graft versus host disease and decompensated cirrhosis.[3] In addition, only a limited number of studies included specific detail about the presence of comorbidities in patients receiving FMT.[3] Strength of recommendations and quality of evidence for patients with comorbidities and at higher risk for FMT adverse effects are as follows:

- FMT should be avoided in those with anaphylactic food allergy (strong recommendation, low-quality evidence).[3]

- FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (weak recommendation, very low-quality evidence).[3]
- FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong recommendation, moderate-quality evidence).[3] Immunosuppressed patients should only receive FMT from donors negative for Epstein–Barr virus (EBV) and cytomegalovirus (CMV) due to risk of severe infection if exposed to EBV or CMV (strong recommendation, very low-quality evidence).[3]
- FMT should be offered to those with recurrent CDI and inflammatory bowel disease (IBD), but patients should be counselled about a small but recognized risk of exacerbation of IBD (strong recommendation, moderate-quality evidence).[3]

This guideline also provides best practice recommendations for FMT donor selection and screening, FMT preparation and administration, and route of FMT administration (upper versus lower gastrointestinal tract).[3] For more information, please refer to the publication.

National Institute for Health and Care Excellence: Fecal Microbiota Transplant for Recurrent CDI

In August 2022, NICE issued guidance for the use of FMT in recurrent CDI.[7] The guideline committee identified and assessed 5 eligible RCTs (n=274) which compared FMT, given via different routes of administration and with a preceding course of antibiotics, with antibiotic treatment.[7] Four RCTs compared FMT and vancomycin and 1 RCT compared FMT with fidoxamicin.[7] Three trials found lower CDI recurrence in the FMT group (range 6% to 10%) compared with the antibiotic group (vancomycin range 62% to 69%, fidaxomicin 46%).[7] However, none of the trials reported statistical significance.[7] Clinical trial evidence shows that FMT treatment is better than antibiotics alone at resolving a CDI in people who have had 2 or more previous infections.[7]

- Recommendation: FMT is recommended as an option to treat recurrent CDI in adults who have had 2 or more previous confirmed episodes.[7]

New Formulations or Indications:

1. A new oral suspension formulation of vancomycin (FIRVANQ) was approved in January 2018.[10] This product is indicated in adults and pediatric patients less than 18 years of age (no clarity regarding lower limit for age provided in prescribing information) for treatment of *C. difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus*.[10] Orally administered vancomycin is not effective for treatment of other types of infections.[10]

2. In January 2020, the FDA expanded the approved population eligible to receive fidaxomicin (DIFICID) to include pediatric patients.[11] Fidaxomicin is now indicated in adult and pediatric patients aged 6 months and older for the treatment of *C. difficile*-associated diarrhea.[11] Pediatric patients must weigh at least 4 kg for the fidaxomicin suspension FDA-approved weight-based dosing parameters.[11] The safety of fidaxomicin in pediatric patients aged 6 months and older was evaluated in a phase 2 single arm trial (n=38).[11] An additional phase 3 RCT (=142) in which fidaxomicin was compared to vancomycin was also submitted to the FDA for expanded approval in pediatric patients.[11] The details of this RCT are summarized in **Table 3.**

Randomized Controlled Trials:

A total of 225 citations were manually reviewed from the initial literature search. After further review, 221 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 4 trials are summarized in **Table 3** below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Guery B., et al[57] Phase 3b/4 RCT MC, OL, PG	1. Fidaxomicin 200 mg orally two times a day x 5 days, followed by 200 mg every other day x 20 days (n=181) 2. Vancomycin 125 mg orally four times a day x 10 days (n=181)	Hospitalized patients with CDI aged 60 yo and older with less than 2 CDI episodes in the previous 3 mos Sites: 86 hospitals in 21 European countries	Sustained clinical cure: resolution of diarrhea at end of therapy and no recurrent CDI 30 days after end of treatment (day 40 for vancomycin and day 55 for fidaxomicin)	Percent of patients with sustained clinical cure 30 days after end of treatment 1. 70% (n=124/177) 2. 59% (n=106/179) Difference: 11% (95% CI 1.0% to 20.7%) OR: 1.62 (95% CI 1.04 to 2.54) P=0.03	-Open label study design -Recurrence was calculated using the entire study population as a denominator; however, earlier trials excluded clinical failures from the denominator -All study sites were located in Europe -Pulsed fidaxomicin dose is not FDA-approved -Patient population excluded people under 60 yo -64% of patients had non-severe CDI -80% of patients were enrolled at diagnosis of first CDI episode
Wolf J., et al[58] Phase 3 RCT MC, PG, investigator-blinded	1. Fidaxomicin 16 mg/kg oral suspension twice daily (ages 0 to 5 yo) or 200 mg twice daily (ages 6 to 18 yo) x 10 days (n=100) 2. Vancomycin 10 mg/kg oral liquid four times a day (ages 0 to 5 yo) or 125 mg four times a day (ages 6 to 17 yo) 10 days (n=48)	Patients less than 18 yo with CDI Sites: 39 sites across the United States, Canada, and Europe Randomized 2:1 Total enrollment = 142 (30 patients < 2 yo)	Confirmed clinical response (resolution of diarrhea) rate 2 days after the end of treatment Secondary endpoint: global cure rate (clinical cure without CDI recurrence) 30 days after end of treatment	Rate of confirmed clinical response 2 days after the end of treatment 1. 77.6% (n=76/98) 2. 70.5% (n=31/44) Adjusted treatment difference: 7.5% (95% CI -7.4% to 23.9%) NS Rate of global cure 30 days after end of treatment 1. 68.4% (n=67/98) 2. 50.0% (n=22/44) Adjusted treatment difference: 18.8% (95% CI 1.5% to 35.3%)	-The study was not designed as a superiority trial and was not powered for this purpose - Single blinded study design (due to different formulations and dosing regimens) -Proportions of treatment-emergent adverse effects were similar for fidaxomicin and vancomycin (74% vs. 75%)
Hvas CL, et al[59] OL, RCT	1. FMT administered via colonoscopy or nasojejunal tube after 4 to 10 days of vancomycin orally 125 mg four times day (n=24)	Adults aged 18 yo and older with recurrent CDI and documented recurrence within 8 weeks after finishing antibiotic (vancomycin or	Combined clinical resolution and a negative PCR test for CD toxin 8 weeks after treatment	Combined clinical resolution and a negative PCR test for CD toxin 8 weeks after treatment 1. 17/24 (71%) 2. 8/24 (33%) 3. 3/16 (19%) 1 vs. 2: p=0.009	-Open label study design -Randomization strategy not described -Small sample size -Study was not powered to detect differences between the 2 antibiotics

	2. Fidaxomicin 200 mg orally twice daily x 10 days (n=24) 3. Vancomycin 125 mg orally four times a day x 10 days (n=16)	fidaxomicin) therapy 1 site in Denmark Total enrollment = 64		1 vs. 3: p=0.001 95% CI not reported	-Not clear why investigators chose vancomycin to precede FMT therapy, but did not compare fidaxomicin + FMT with the combination treatment of vancomycin + FMT
Mikamo H, et al[60] Phase 3 RCT MC, NI, DB, PG	1. Fidaxomicin 200 mg orally twice daily x 10 days (n=106) 2. Vancomycin 125 mg orally four times a day x 10 days (n=109)	Hospitalized patients with CDI aged ≥20 years who had not received antibiotic treatment for CDI, or had treatment failure after ≥3 days of metronidazole t herapy Total enrollment = 212 Sites: 82 hospitals in Japan	Global CDI cure rate (proportion of patients cured at end of treatment with no recurrence during 28-day follow-up) Lower limit of NI margin = -10%	Global CDI cure rate 1. n=70/104 (67.3%) 2. n=71/108 (65.7%) Difference: 1.2% 95% CI -11.3 to -13.7 Non-inferiority was not demonstrated	-Non-inferiority trial -Limited to sites in Japan -77% of patients had mild to moderate CDI -85% of patients were enrolled at diagnosis of first CDI episode and were inpatients, cannot extrapolate results to outpatient population
Abbreviations: CD = *Clostridioides difficile*; CDI = *Clostridioides difficile* infection; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; FMT = fecal microbiota transplantation; mos = months; MC = multi-center; NI = non-inferiority; NS = non-significant; OL = open label; OR = odds ratio; PCR = polymerase chain reaction; PG = parallel group; RCT = randomized controlled trial; yo = years old					

NEW DRUG EVALUATION: Fecal Microbiota, live-jslm (REBYOTA)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Fecal microbiota, live-jslm (REBYOTA), a live biotherapeutic suspension for rectal administration, is indicated for the prevention of recurrent CDI in adults aged 18 years and older following antibiotic treatment for recurrent CDI.[8] The FDA granted Breakthrough Therapy status, Fast Track, and Orphan Drug designations for this new biotherapeutic in November 2022.[61] The commercial formulation of fecal microbiota suspension is FDA-regulated as a biologic drug.[9] It is not indicated for treatment of CDI.[8] Safety and efficacy in pediatric patients have not been established.[8] The recommended dose is 150 mL administered rectally 24 to 72 hours after the last dose of antibiotics for CDI treatment.[8] The product is manufactured from human fecal matter sourced from qualified donors and tested for transmissible pathogens.[8]

The FDA granted approval of fecal microbiota based on findings from the PUNCH CD3 trial, a phase 3, multicenter, double-blinded, placebo-controlled RCT.[9] Forty-one study sites in the United States and Canada participated in this RCT.[9] Patients (n=267) were enrolled and randomized 2:1 to receive a single-dose of fecal microbiota enema (n=180) or a single-dose of placebo (n=87) 24 to 72 hours after the last dose of the CDI antibiotic regimen.[61] Eligible patients met one of the following parameters: 1) had one or more recurrent CDI episodes with completion of a recent SOC 10-day antibiotic regimen or 2) had experienced 2 or more severe CDI episodes resulting in hospitalization within the previous year.[61] In addition, within 30 days before enrollment, patients were required to have a positive stool test for the presence of *C. difficile* with the capability to produce toxins.[61] Patients were excluded if they had a known history of severe CDI, inflammatory bowel disease, irritable bowel syndrome, celiac disease, colostomy, active colitis, continued diarrhea despite antibiotic therapy, required antibiotic therapy for another condition, or had received a previous FMT.[61]

Patients were stratified by antibiotic use at enrollment (vancomycin monotherapy, vancomycin in combination with either metronidazole and/or fidaxomicin, fidaxomicin monotherapy, or other antibiotic).[61] The primary endpoint was treatment success, defined as absence of recurrent CDI diarrhea (passage of 3 or more unformed stools in 24 hours for at least 2 days) 8 weeks after treatment.[61] Secondary endpoints included sustained clinical response rate (recurrent CDI successfully treated and no new CDI episodes 6 months after completed treatment) and the incidence of adverse effects.[61] Treatment with open-label fecal microbiota enema was an option for patients who experienced treatment failure within 8 weeks. A total of 65 (25%) patients including 23% in the fecal microbiota arm and 28% in the placebo arm were designated as treatment failures and received one dose of open-label fecal microbiota enema.[9]

For PUNCH CD3, a total of 320 study participants were screened for study inclusion.[61] Thirty-one participants did not meet inclusion criteria or withdrew consent prior to receiving treatment.[61] The intention-to-treat (ITT) population (n=289) was defined as all randomized patients allocated to the 2 treatment groups; if participants withdrew prior to receiving blinded treatment they were not included in the ITT analysis.[61] The modified intention-to-treat (mITT) population (n=262) was defined as all participants who successfully completed treatment and were evaluated for the primary endpoint at 8 weeks.[61] The mITT population was pre-specified as the primary analysis population.[9] The per protocol (PP) population (n=245) was defined as all participants who successfully completed treatment and did not discontinue the trial for reasons not related to CDI or protocol violations.[61] Baseline characteristics were comparable between the 2 treatment arms, however, the placebo arm had a higher proportion of participants younger than 65 years of age than the fecal microbiota arm (62% vs. 51%, respectively).[61] The median age of study participants was 63 years, most participants were White (92.1%), and female (68.5%).[61] Most participants received vancomycin (88%) prior to treatment with fecal microbiota as that was the SOC antibiotic during the time period of the study (conducted July 2017 to April 2020). [6]

In the PUNCH CD3 trial, mITT population results for the primary outcome were not significant, as 71.2% treated with fecal microbiota enema and 62.4% treated with placebo had treatment success (treatment difference: 8.8%; 95% CI -3.4 to 21.1; p=0.15).[61] The investigators found it was challenging to recruit enough study participants (due to the widespread availability of compounded FMT products) so in an interim assessment, an agreement was reached with FDA personnel to permit data from one previous phase 2 trial (PUNCH CD2) to be used in the statistical analysis of PUNCH CD3 results.[9] The PUNCH CD2 trial (n=133) was similar to PUNCH CD3 in study design, product formulation, and treatment success definitions.[9] However, in PUNCH CD2, 1 and 2 doses of fecal microbiota enema administered 1 week apart were compared to placebo. Also, the PUNCH CD2 trial enrolled participants who had 2 or more CDI recurrences compared with PUNCH CD3, which enrolled participants with at least one or more CDI recurrences.[9,61] The primary efficacy analysis in PUNCH CD2 was the treatment success rate after 2 doses of fecal microbiota versus 2 doses of placebo in the ITT population, which was not significant (55.6% vs. 43.2%, respectively, treatment difference = 12.4%; 95% CI -8.2 to 33; P=0.243).[9] A secondary outcome analysis, showed a superior response to one dose fecal microbiota vs. placebo (p=0.047); therefore, a single dose of fecal microbiota was selected for subsequent studies.[9]

Data from the 1-dose fecal microbiota arm compared with placebo (n=82) in PUNCH CD2 was used in Bayesian statistical analysis of the PUNCH CD3 results.[61] The investigators prespecified two superiority thresholds: (1) posterior probability of superiority > 0.999 was selected to control the nominal type I error rate without borrowing at one-sided 0.00125; and (2) posterior probability of superiority > 0.975 was selected to control the nominal type I error rate without borrowing at one-sided 0.025.[61] In the statistical analysis that took into account both studies, the overall estimated rate of success in preventing recurrent CDI through 8 weeks was higher in the mITT fecal microbiota group that received 1 dose (70.6%) than in the 1-dose placebo group (57.5%) with an estimated treatment effect of 13.1% (95% CI 2.3 to 24%) and a posterior probability of superiority of 0.991.[9] The details of PUNCH CD3 and PUNCH CD2 RCTs are described and evaluated below on **Table 5.**

The small number of non-White patients and lack of participants with irritable bowel syndrome, inflammatory bowel disease, and immunocompromising conditions limits the ability to generalize the data from PUNCH CD3.[61] An open-label study (PUNCH CD3-OLS) is ongoing, which includes a more diverse recurrent CDI population compared with prior fecal microbiota studies and allows enrollment of patients with immunocompromised conditions and chronic conditions such as irritable bowel syndrome or inflammatory bowel disease.[61] In PUNCH CD3, most of the patients received vancomycin (88%) and only 6% of patients received fidaxomicin before administration of fecal microbiota. More data is needed to assess the efficacy of fecal microbiota administration after completion of a fidaxomicin regimen for recurrent CDI. Of note, the placebo response in PUNCH CD3 was higher than expected. The investigators postulated that treatment success rates can be influenced by the diagnostic modality for confirming CDI.[61] Although the polymerase chain reaction (PCR) assay is the most commonly used diagnostic tool in clinical practice in the U.S., and was used in over 70% of PUNCH CD3 participants, it can result in a false positive result.[61] This may lead to the inclusion of patients who do not actually have CDI and therefore also impact treatment response rates.[61] Another possible explanation for the higher placebo effect is that approximately one-third of PUNCH CD3 participants were enrolled after only one CDI recurrence.[61] As the risk of recurrence increases with each subsequent infection, some PUNCH CD3 placebo participants may have had a lower risk of recurrence because of less severe dysbiosis.[61] There is insufficient data comparing the REBYOTA enema with unlicensed, compounded, forms of FMT (i.e. manipulated whole stool in capsule form). Additional data is also needed to assess long term safety and use in patients with severe CDI.

Clinical Safety:
Because rectal fecal microbiota is manufactured from human fecal matter is carries the risk of transmitting infectious agents and may contain food allergens.[8] The potential for fecal microbiota to cause adverse effects due to food allergens is unknown.[8] The most commonly reported adverse events reported after a single fecal microbiota dose compared with placebo in the phase 3 PUNCH CD3 trial were abdominal pain (8.9% vs. 6.9%), diarrhea (7% vs. 3.4%), abdominal distention (3.9% vs. 2.3%), flatulence (3.3% vs. 0) and nausea (3.3% vs. 1%).[9] Most adverse events occurred during the first 2 weeks of treatment.[9]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Resolution of CDI-associated diarrhea without CDI recurrence within 8 weeks
2) Sustained treatment response (no CDI 6 months after last dose)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Treatment success (absence of CDI diarrhea within 8 weeks of treatment)

Table 4. Pharmacology and Pharmacokinetic Properties[8]

Parameter	
Mechanism of Action	Not established: theoretical supposition that biotherapeutic product repopulates and restores diversity of gut microbiome to suppress *C. difficile* overgrowth
Oral Bioavailability, Distribution, and Protein Binding	Not Applicable
Elimination, Half-Life and Metabolism	

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. Khanna S, et al.[9,61] PUNCH CD3 Phase 3, MC, DB, PC, RCT	1. Fecal microbiota 150 ml enema x 1 dose 24 to 72 hrs after antibiotic washout 2. Placebo (saline) enema x 1 dose 24 to 72 hrs after antibiotic washout	Demographics of the Safety Population: 1. Median age: 63 yo 2. Age ≥ 65 yo: 46% 3. Female: 69% 4. White: 92% 5. Recent antibiotic use prior to enrollment: -Vancomycin 88% -Fidaxomicin 6% -Vancomycin in combination 3% -Other 3% 6. Number of CDI episodes ≤ 3: 64% Key Inclusion Criteria: -Adults ≥ 18 yo with ≥ 1 episode of rCDI and completion of 1 round of SOC antibiotics OR ≥ 2 episodes of severe CDI resulting in hospitalization -Currently taking antibiotics to control rCDI symptoms (<3 loose stools per day) -Positive stool test for the presence of toxigenic *C. difficile* within 30 days of study enrollment Key Exclusion Criteria: -Refractory CDI	**PUNCH CD3** ITT: 1. 193 2. 96 mITT: Subjects excluded from ITT analysis due to study withdrawal prior to treatment 1. 177 2. 85 Attrition: 1. 16 (8%) 2. 11 (11%) Safety Population: 1. 180 2. 87 **Matched group from both trials** PUNCH CD2 (mITT):	Primary Endpoint: Percent of patients with treatment success (no CDI diarrhea) at 8 weeks ITT population: 1.126 (70.0%) 2.53 (60.9%) Difference: 9.1 95% CI -3.2 to 21.3 P =0.139 mITT population: 1. 126 (71.2%) 2. 53 (62.4%) Difference: 8.8% 95% CI -3.4 to 21.1 P= 0.150 Matched mITT populations from PUNCH CD2 and PUNCH CD3 (Bayesian analysis): 1. 151 (70.6%) 2. 72 (57.50%) Difference: 13.1% 95% CI 2.3 to 24 Posterior probability of superiority of 1 vs. 2 = 0.975	N/A N/A N/A 13.1% /8	TEAEs at 8 weeks post-treatment 1. 79 (56.8%) 2. 30 (47.6%) Serious TEAEs at 8 weeks post-treatment 1. 6 (4.3%) 2. 3 (4.8%) Serious TEAEs at 6 mos post-treatment 1. 15 (8.3%) 2. 6 (6.9%) TEAEs leading to withdrawal 1. 3 (1.7%) 2. 0 95% CI NR for all	N/A N/A N/A N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 2:1 to active treatment vs. placebo. Method of randomization not clear. Baseline characteristics balanced for most demographic parameters, except placebo group enrolled more people aged 65 yo and younger. Performance Bias: Low. Double blinded study design. Fecal microbiota and placebo were both supplied in equal volumes in a brown enema bag with an opaque sleeve to cover bag and tubing to preserve blinding. Possible that side effects from active treatment could have unblinded treatment assignment. Detection Bias: Unclear. Treatment success determined by an independent blinded adjudication committee. Participants recorded daily symptoms in a diary up to 7 days after treatment, which may have been subject to recall bias. Attrition Bias: Low. Attrition was similar between study groups. The most common reason for study withdrawal was withdrawal by the patient prior to treatment. Reporting Bias: Unclear. Study protocol available online. All outcomes reported as described. Decision to include Phase 2 data was made when recruitment of sufficient patients was identified as an issue in an interim analysis. Patients in Phase 2 RCT had a median of 4 CDI recurrences, while most patients in PUNCH CD3 had less than 3 CDI recurrences. Other Bias: High. Study was financially supported by the manufacturer. Manufacturer also involved in data collection, analysis, and interpretation of results. Several authors reported financial support via grants or contracts from the manufacturer.

		-Chronic diarrhea -Celiac disease -Short gut syndrome -Continued CDI diarrhea despite antibiotic treatment -Previous fecal transplant -Colitis -Irritable bowel syndrome -Inflammatory bowel disease -Compromised immune system -Taking > 20 mg of prednisone	1. 39 2. 43 Total from both trials (mITT): 1. 216 2. 128	Secondary Endpoint: Percent of ITT PUNCH CD3 patients without rCDI at 6 mos (sustained clinical response) 1. 116 (64.4%) 2. 48 (55.2%) Difference: 9.3% 95% CI -3.3 to 21.9 P=0.145 Percent of mITT PUNCH CD3 patients without rCDI at 6 mos (sustained clinical response) 1. 116 (65.5%) 2. 48 (56.5%) Difference: 9.1 95% CI -3.5 to 21.7 P=0.156				**Applicability**: Patient: Enrolled patients were primarily White. Excluded patients with severe CDI, irritable bowel syndrome, and those who were immunocompromised. Cannot apply this data to those populations. This data is most appliable to the 88% of patients who received vancomycin. Only 6% of enrolled patients received fidaxomicin, and more data is needed to assess applicability of these results to these patients. Fidaxomicin appears to be more effective than vancomycin in preventing CDI recurrence. Intervention: Administration of 1 dose of fecal microbiota was shown to be effective in preventing rCDI in phase 2 clinical trials. FDA approved dose is 1 dose based on combined results from Phase 2 and Phase 3 RCTs. Comparator: Placebo was an effective comparator for a novel agent. Comparison to current standard of care including fidaxomicin or compounded FMT for rCDI is unknown. Guideline recommendations were updated in 2021, after completion of this study in 2020. Outcomes: Treatment success (defined as symptom resolution) at 8 weeks is a clinically relevant endpoint as defined in guidelines. Setting: 36 sites in the US and 5 sites in Canada. Conducted from 7/2017 to 4/2020.
2. Dubberke ER, et al.[9,62] PUNCH CD2 Phase 2, MC, DB, PC, RCT	1. Fecal microbiota 150 ml enema x 2 doses 7 days apart, 24 to 48 hrs after antibiotic washout 2. Placebo (saline) enema x 2 doses 7 days apart, 24 to 48 hrs after antibiotic washout 3. Fecal microbiota 150 ml enema x 1	Demographics: 1. Mean age: 64 yo 2. Female: 62% 3. White: 98 % 4. Antibiotic use -Vancomycin 90% -Fidaxomicin 4% -Metronidazole 5% 5. Median number of CDI episodes: 4 Key Inclusion Criteria: -Adults ≥ 18 yo with ≥ 2 episodes of rCDI and completion of 2 rounds of SOC antibiotics OR ≥ 2 episodes of severe CDI resulting in hospitalization	ITT: 1. 45 2. 44 3. 44 mITT: 1. 40 2. 43 3. 38 Attrition: 1. 5 (11%) 2. 1 (2.3%) 3. 6 (13.6%)	Primary Endpoint: Percent of ITT patients with treatment success (no rCDI diarrhea) at 8 weeks in Group 1 (fecal microbiota x 2 doses) versus Group 2 (placebo x 2 doses) 1. 25 (55.6%) 2. 19 (43.2%) Difference: 12.4% 95% CI -8.2 to 33 P=0.243 Percent of mITT patients with treatment success at 8 weeks in Group 1 versus Group 2	N/A N/A	All AEs 7 days post-treatment 1. 34 (81%) 2. 35 (79.5%) 3. 29 (69%) TEAEs through 24 mos post-treatment 1. 34 (81%) 2. 38 (86.4%) 3. 33 (78.6%) Severe TEAEs through 24 mos post-treatment 1. 7 (16.7%)	N/A N/A N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 using permuted blocks stratified by antibiotic regimen. Baseline characteristics balanced between treatment groups. Performance Bias: Low. Study participants, investigators, and site personnel were blinded to treatment assignment. Detection Bias: Unclear. Fecal microbiota and placebo were both supplied in a brown enema bag with an opaque sleeve to cover bag and tubing to preserve blinding. Participants recorded daily symptoms in a diary up to 7 days after treatment, which may have been subject to recall bias. Treatment success determined by an independent blinded adjudication committee. Attrition Bias: High. Attrition was higher in active comparator arms versus placebo. Death was the reason most patients (n=6) withdrew from the study in both fecal microbiota arms (2 doses: 7%; 1 dose: 7%). Death was related to pre-existing condition, not treatment

	dose plus 1 dose of placebo 7 days apart, 24 to 48 hrs after antibiotic washout	-Currently taking antibiotics to control rCDI symptoms (< 3 stools per day) -Positive stool test for the presence of toxigenic *C. difficile* within 60 days of study enrollment Key Exclusion Criteria: -Chronic diarrhea -Celiac disease -Short gut syndrome -Continued CDI diarrhea despite antibiotic treatment -Previous fecal transplant -Irritable bowel syndrome -Colitis -Inflammatory bowel disease -Compromised immune system -Taking ≥ 20 mg or equivalent of prednisone		1. 25 (62.5%) 2. 19 (44.2%) Difference: 18.3% 95% CI -2.8 to 39.4 P=0.095 Secondary Endpoint: Percent of ITT patients with treatment success (no rCDI) at 8 weeks in Group 2 (placebo x 2 doses) versus Group 3 (fecal microbiota x 1 dose plus 1 dose of placebo) 2. 19 (43.2%) 3. 25 (56.8%) Difference: 13.6% 95% CI -7.1 to 34.3 P=0.201 Percent of mITT patients with treatment success at 8 weeks in Group 2 versus Group 3 2. 19 (44.2%) 3. 25 (65.8%) Difference: 21.6% 95% CI 0.4 to 42.8 P = 0.051	N/A N/A	2. 4 (9.1%) 3. 5 (11.9%) TEAEs leading to withdrawal 1. 14 (31.1%) 2. 9 (20.5%) 3. 19 (43.2%) Death	N/A	(health decline, renal failure, respiratory failure, resistant bacteremia). Other reasons for study withdrawal included investigator withdrawal, loss to follow-up, and withdrawal by patient. Reporting Bias: Low. Clinical protocol available online. Outcomes reported as planned. Other Bias: High. Study was financially supported by the manufacturer. Six authors serve on the advisory board of the manufacturer. **Applicability**: Patient: Enrolled patients were primarily White. Excluded patients with irritable bowel syndrome, inflammatory bowel disease, and those who were immunocompromised. Much higher proportion of patients received vancomycin compared with fidaxomicin (90% vs. 4%). Need for data to assess efficacy of fecal microbiota after rCDI treatment with fidaxomicin. Intervention: Dose finding Phase 2 trial: 1 vs. 2 doses of fecal microbiota enema were compared to placebo. Primary outcome was 2 dose regimen vs. placebo, which was not significant. Comparator: Placebo was a useful comparator for a novel therapy in a Phase 2 RCT. Outcomes: Treatment success at 8 weeks, as defined by guidelines. Setting: 19 sites in the US and 2 sites in Canada

Abbreviations: AEs = adverse effects; ARR = absolute risk reduction; CD = *Clostridioides difficile*; CDI = *Clostridioides difficile* infection; CI = confidence interval; DB = double blind; FMT = fecal microbiota transplantation; hrs = hours; ITT = intention to treat; mos = months; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PC = placebo controlled; RCT = randomized controlled trial; rCDI = recurrent *Clostridioides difficile* infection; SEAs = serious adverse effects; SOC = standard of care; TEAEs = treatment emergent adverse effects; US = United States; yo = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
metronidazole	FLAGYL	ORAL	CAPSULE	Y
metronidazole	METRONIDAZOLE	ORAL	CAPSULE	Y
metronidazole	FLAGYL	ORAL	TABLET	Y
metronidazole	METRONIDAZOLE	ORAL	TABLET	Y
vancomycin HCl	VANCOMYCIN HCL	INTRAVEN	VIAL	Y
vancomycin HCl	VANCOCIN HCL	ORAL	CAPSULE	Y
vancomycin HCl	VANCOMYCIN HCL	ORAL	CAPSULE	Y
bezlotoxumab	ZINPLAVA	INTRAVEN	VIAL	N
fidaxomicin	DIFICID	ORAL	SUSP RECON	N
fidaxomicin	DIFICID	ORAL	TABLET	N
vancomycin HCl	FIRVANQ	ORAL	SOLN RECON	N
vancomycin HCl	VANCOMYCIN HCL	ORAL	SOLN RECON	N
vancomycin HCl	VANCOMYCIN HCL	INTRAVEN	VIAL	

Appendix 2: Abstracts of Comparative Clinical Trials

***Extended-Pulsed Fidaxomicin Versus Vancomycin for Clostridium Difficile Infection In Patients 60 Years And Older (EXTEND): A Randomised, Controlled, Open-Label, Phase 3b/4 Trial.*[57]**

Background: Clostridium difficile infection causes severe complications and frequently recurs. An extended-pulsed fidaxomicin regimen might facilitate sustained clinical cure by prolonging C difficile suppression and supporting gut microbiota recovery. We aimed to compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin.

Methods: In this randomised, controlled, open-label, superiority study, we recruited hospitalized adults aged 60 years and older with confirmed *C. difficile* infection at 86 European hospitals. Patients were randomly assigned (1:1) using an interactive web response system to receive extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25) or vancomycin (125 mg oral capsules, four times daily on days 1–10), stratified by baseline C difficile infection severity, cancer presence, age (≥75 years vs <75 years), and number of previous C difficile infection occurrences. The primary endpoint was sustained clinical cure 30 days after end of treatment (day 55 for extended-pulsed fidaxomicin and day 40 for vancomycin), assessed in all randomised patients who met the inclusion criteria and received at least one dose of study medication (modified full analysis set). Adverse events were assessed in all patients who received at least one dose of study drug. The study is registered with ClinicalTrials.gov, number NCT02254967.

Findings: Between Nov 6, 2014, and May 5, 2016, 364 patients were enrolled and randomly assigned to receive extended-pulsed fidaxomicin or vancomycin. 362 patients received at least one dose of study medication (181 in each group). 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI 1·0–20·7], p=0·030; odds ratio 1·62 [95% CI 1·04–2·54]). Incidence of treatment-emergent adverse events did not differ between extended-pulsed fidaxomicin (121 [67%] of 181) and vancomycin (128 [71%] of 181) treatment arms. One death in the vancomycin arm was considered by the investigator to be related to study drug.

Interpretation: Extended-pulsed fidaxomicin was superior to standard-dose vancomycin for sustained cure of C difficile infection, and, to our knowledge, extended-pulsed fidaxomicin recurrence rates in this study are the lowest observed in a randomised clinical trial of antibiotic treatment for C difficile infection.

Funding: Astellas Pharma, Inc.

***Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with Clostridioides (Clostridium) difficile Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE)*[58]**

Background: Fidaxomicin, a narrow-spectrum antibiotic approved for Clostridioides (Clostridium) difficile infection (CDI) in adults, is associated with lower rates of recurrence than vancomycin; however, pediatric data are limited. This multicenter, investigator-blind, phase 3, parallel-group trial assessed the safety and efficacy of fidaxomicin in children.

Methods: Patients aged <18 years with confirmed CDI were randomized 2:1 to 10 days of treatment with fidaxomicin (suspension or tablets, twice daily) or vancomycin (suspension or tablets, 4 times daily). Safety assessments included treatment-emergent adverse events. The primary efficacy end point was confirmed clinical response (CCR), 2 days after the end of treatment (EOT). Secondary end points included global cure (GC; CCR without CDI recurrence) 30 days after EOT (end of study; EOS). Plasma and stool concentrations of fidaxomicin and its active metabolite OP-1118 were measured.

Results: Of 148 patients randomized, 142 were treated (30 <2 years old). The proportion of participants with treatment-emergent adverse events was similar with fidaxomicin (73.5%) and vancomycin (75.0%). Of 3 deaths in the fidaxomicin arm during the study, none were CDI or treatment related. The rate of CCR at 2 days after EOT was 77.6% (76 of 98 patients) with fidaxomicin and 70.5% (31 of 44) with vancomycin, whereas the rate of GC at EOS was significantly higher in participants receiving fidaxomicin (68.4% vs 50.0%; adjusted treatment difference, 18.8%; 95% confidence interval, 1.5%-35.3%). Systemic absorption of fidaxomicin and OP-1118 was minimal, and stool concentrations were high.

Conclusions: Compared with vancomycin, fidaxomicin was well tolerated and demonstrated significantly higher rates of GC in children and adolescents with CDI.

***Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection*[59]**

Background: Fecal microbiota transplantation (FMT) is recommended for treatment of recurrent Clostridium difficile infection (rCDI). We performed a single-center randomized trial to compare the effects of FMT with those of fidaxomicin and vancomycin.

Methods: We studied consecutive adults with rCDI seen at a gastroenterology clinic in Denmark from April 5, 2016 through June 10, 2018. Patients were randomly assigned to a group that received FMT, applied by colonoscopy or nasojejunal tube, after 4-10 days of vancomycin (125 mg 4 times daily; FMTv; n = 24), 10 days of fidaxomicin (200 mg twice daily; n = 24), or 10 days of vancomycin (125 mg 4 times daily; n = 16). Patients who had rCDI after this course of treatment and patients who could not be randomly assigned to groups were offered rescue FMTv. The primary outcome was combined clinical resolution and a negative result from a polymerase chain reaction test for Clostridium difficile (CD) toxin 8 weeks after the allocated treatment. Secondary end points included clinical resolution at week 8.

Results: All 64 patients received their assigned treatment. The combination of clinical resolution and negative results from the test for CD were observed in 17 patients given FMTv (71%), 8 patients given fidaxomicin (33%), and 3 patients given vancomycin (19%; P = .009 for FMTv vs fidaxomicin; P = .001 for FMTv vs vancomycin; P = .31 for fidaxomicin vs vancomycin). Clinical resolution was observed in 22 patients given FMTv (92%), 10 patients given fidaxomicin (42%), and 3 patients given vancomycin (19%; P = .0002; P < .0001; P = .13). Results did not differ significantly between patients who received FMTv as their initial therapy and patients who received rescue FMTv. There was 1 serious adverse event that might have been related to FMTv.

Conclusions: In a randomized trial of patients with rCDI, we found the FMTv combination superior to fidaxomicin or vancomycin based on end points of clinical and microbiological resolution or clinical resolution alone. ClinicalTrials.gov, number NCT02743234.

***Efficacy And Safety of Fidaxomicin For The Treatment Of Clostridioides (Clostridium) Difficile Infection In A Randomized, Double-Blind, Comparative Phase III Study In Japan*[60]**

We assessed the efficacy and safety of fidaxomicin, a narrow-spectrum macrocyclic antibiotic, for treating inpatients with Clostridioides (Clostridium) difficile infection (CDI) in Japan. The objective was to demonstrate the non-inferior efficacy of fidaxomicin versus vancomycin.

This Phase III, vancomycin-controlled, double-blind, parallel-group study enrolled adults with CDI. Patients were randomly assigned to receive fidaxomicin (200 mg twice daily, orally) or vancomycin (125 mg four-times daily, orally) for 10 days. The primary endpoint was global cure rate of CDI (proportion of patients cured at end of treatment with no recurrence during 28-day follow-up). Non-inferiority margin of 10% was pre-specified.

Two-hundred and twelve patients were randomized and received treatment at 82 hospitals. Global cure rate was 67.3% (70/104) with fidaxomicin and 65.7% (71/108) with vancomycin: difference 1.2% [95% confidence interval (CI) −11.3–13.7]. Non-inferiority was not demonstrated. Post-hoc analysis in full analysis set patients who received at least 3 days' treatment revealed a higher global cure rate for fidaxomicin [70/97 (72.2%)] than vancomycin [71/106 (67.0%)]: difference 4.6% (95% CI −7.9–17.1). Recurrence rate in the full analysis set for recurrence was lower in fidaxomicin- [17/87 (19.5%)] than vancomycin-treated [24/95 (25.3%)] patients. Adverse event incidences and profiles were similar for both treatments.

Though non-inferiority was not demonstrated for fidaxomicin versus vancomycin, global cure rate was numerically higher and recurrence rate lower for fidaxomicin than vancomycin. Fidaxomicin could be an option for the treatment of CDI in an era of reduced antibiotic susceptibility, and to reduce the incidence of recurrence in Japanese patients.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to January Week 4 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to February 07, 2023

1	clostridium difficile.mp. or exp Clostridium difficile/ or Clostridioides difficile.mp.	14511
2	vancomycin.mp. or Vancomycin/	26824
3	metronidazole.mp. or Metronidazole/	12917
4	fidaxomicin.mp.	538
5	bezlotoxumab.mp.	116
6	Fecal Microbiota Transplantation/ or fecal microbiota.mp.	5688
7	2 or 3 or 4 or 5 or 6	43959
8	1 and 7	3500
9	limit 8 to (english language and humans and yr="2018 -Current")	1160
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	225

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

REBYOTA™ (fecal microbiota, live - jslm) suspension, for rectal use
Initial U.S. Approval: 2022

INDICATIONS AND USAGE

REBYOTA is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI. (1)

Limitation of Use:
REBYOTA is not indicated for treatment of CDI.

DOSAGE AND ADMINISTRATION

For rectal administration only.

Administer REBYOTA 24 to 72 hours after the last dose of antibiotics for CDI. (2)

Administer a single dose of 150 mL rectally of REBYOTA. (2)

DOSAGE FORMS AND STRENGTHS

Suspension. A single dose is 150 mL. (3)

CONTRAINDICATIONS

Severe allergic reactions (e.g. anaphylaxis) to any component of REBYOTA. (4)

ADVERSE REACTIONS

The most commonly reported (≥ 3%) adverse reactions occurring in adults following a single dose of REBYOTA were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%) (Table 1).

To report SUSPECTED ADVERSE REACTIONS, contact Ferring Pharmaceuticals Inc. at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. (6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 11/2022

Prevention of Recurrent *Clostridioides difficile*-Associated Infection

Goal(s):

- To optimize appropriate prevention of recurrent *Clostridioides difficile*-associated infection (CDI). Recurrent CDI is defined by Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as an episode of CDI that occurs less than 8 weeks after the onset of a previous CDI episode, if CDI symptoms from the previous episode were resolved.

Length of Authorization:

- Bezlotoxumab (ZINPLAVA): One time infusion
- Fecal microbiota, live-jslm (REBYOTA): One-time rectal administration

Requires PA:

- Drugs for prevention of *Clostridioides difficile* recurrence such as:
  - Bezlotoxumab for intravenous infusion (physician administered and pharmacy claims)
  - Fecal microbiota, live-jslm suspension for rectal administration (physician administered and pharmacy claims)
  - Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the indication match the FDA-approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for an FDA approved age (e.g., 18 years or older)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for bezlotoxumab?	**Yes**: Go to #5	**No**: Go to #7
5. Is this recurrent of *Clostridioides difficile*-associated infection (CDI) within 6 months of CDI **OR** Is the patients presenting with a primary CDI episode and has other risk factors for CDI recurrence (such as age ≥65 years, immunocompromised host, or severe CDI on presentation)?* *Per 2021 IDSA/SHEA guidance[1]	**Yes**: Go to #6	**No**: Pass to RPh. Deny; medical appropriateness
6. Is the patient currently receiving vancomycin or fidaxomicin?	**Yes**: Approve for one dose	**No**: Pass to RPh. Deny; medical appropriateness
7. Is this the second or more recurrence of a Clostridioides difficile-associated infection?* *Per 2021 ACG and 2022 NICE guidance[2,3]	**Yes:** Go to #8	**No**: Pass to RPh. Deny; medical appropriateness
8. Will the patient have recently completed a 10-day course of vancomycin or fidaxomicin prior to starting therapy?	**Yes**: Approve for one course of therapy. (For the fecal microbiota enema, 1 dose is the FDA-approved course of therapy).	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *6/23 (DM)*
Implementation: *TBD*

1. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021; 73(5):e1029-e1044.

2. Kelly CR, Fischer M, Allegretti JR, et al. American College of Gastroenterology Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology. 2021; 116(6):1124-1147.
3. National Institute for Health and Care Excellence (NICE): Fecal microbiota transplant for recurrent Clostridioides difficile infection. August 31, 2022. https://www.nice.org.uk/guidance/mtg71 Accessed February 27, 2023.

Fidaxomicin (Dificid®) - RETIRE

Goal(s):

- To optimize appropriate treatment of *Clostridioides difficile*-associated infection.

Length of Authorization:

- 10 days

Requires PA:

- Fidaxomicin from pharmacy claims

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of *Clostridioides difficile*-associated infection (CDI)?	**Yes:** Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have severe, complicated CDI (life-threatening or fulminant infection or toxic megacolon)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 10 days

P&T / DUR Review: *5/18 (DM); 5/15 (AG); 4/12*
Implementation: *7/1/18; 10/15; 7/12*

Bezlotoxumab (Zinplava™)- RETIRE

Goal(s):

- To optimize appropriate prevention of recurrent *Clostridium difficile*-associated infection.

Length of Authorization:

- One time infusion

Requires PA:

- Bezlotoxumab (physician administered and pharmacy claims)

Covered Alternatives:

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

Approval Criteria		
1.What diagnosis is being treated?	Record ICD10 code	
2.Does the patient have a diagnosis of recurrent *Clostridium difficile*-associated infection (CDI)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
3.Is the patient currently receiving vancomycin or fidaxomicin?	**Yes**: Approve for one dose	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *5/18(DM)*
Implementation: *7/1/18*