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, August 6th, 2020 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	T. Douglass (OHA)
1:15 PM	II. CONSENT AGENDA TOPICS	J. Slater (Chair)

A. Quarterly Utilization Reports
B. Antipsychotic Class Update with Caplyta™ (lumateperone) New Drug Evaluation
C. Vascular Endothelial Growth Factors Class Update with Beovu® (brolucizumab-dbll) New Drug Evaluation
D. ADHD Literature Scan
E. Immune Globulin Drug Use Evaluation
F. Oncology Policy Updates
G. Orphan Drug Policy Updates
   1. Public Comment

III. DUR ACTIVITIES

1:20 PM	A. ProDUR Report	R. Holsapple (DXC)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)

   1. Biosimilar Medications: Key Considerations for Providers
   2. Coronavirus Management: Evidence for Treatment and Drug Shortage Updates

IV. PREFERRED DRUG LIST NEW BUSINESS

1:30 PM	A. Cardiovascular Outcomes of Newer Diabetes Drugs DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
1:55 PM	B. Non-statin Drugs for Dyslipidemia Class Update 1. Class Update/Prior Authorization Criteria 2. Nexletol™ (bempedoic acid) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:15 PM	C. Multiple Sclerosis DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:35 PM	D. Serotonin Agonists (formerly Triptans) Class Update 1. Class Update/Prior Authorization Criteria 2. Reyvow™ (lasmiditan) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:55 PM	BREAK	
3:00 PM	E. CGRP Inhibitors DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:20 PM	F. Topical Analgesics and Anesthetics Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:35 PM	G. Antacids (Proton Pump Inhibitors and H2 Receptor Antagonists) Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU
3:50 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
Tracy Klein, PhD, FNP	Public	Nurse Practitioner	Portland	December 2020
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director	Coos Bay	December 2020
William Origer, MD	Physician	Residency Faculty	Albany	December 2020
James Slater, PharmD	Pharmacist	Pharmacy Director	Beaverton	December 2020
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021
Patrick DeMartino, MD, MPh	Physician	Pediatrician	Portland	December 2022
Dave Pass, MD	Physician	Medical Director	West Linn	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 04, 2020 1:00 - 5:00 PM

Via Zoom webinar

MEETING MINUTES

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

Members Present: Mark Helm, MD, MBA, FAAP; Caryn Mickelson, PharmD; Russell Huffman, DNP, PMHNP; Tracy Klein, PhD, FNP; William Origer, MD, James Slater, PharmD; Patrick DeMartino, MD, MPh; Stacy Ramirez, PharmD; Cathy Zehrung RPh; David Pass, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Andrew Gibler, PharmD; Dean Haxby PharmD; Megan Herink, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston, JD; Brandon Wells; Jennifer Bowen

Audience: Alexandra Lachmann, Gilead; Amy Hamdan; Andrea Willcuts, Takeda; Andrew Yu, Novartis; Bill McDougall, Biogen; **Brandon Yip, Sanofi-Genzyme*;** Brook Goobic, Vertex; Bruce Wallace, Azurity; Carmen Oliver, BioHaven; Chelsea Leroue, PhD, BioHaven; Chi Kohlhoff, Viela Bio; Chris DeSimone; Christina Hartmann, Jazz Pharma; Crystal Henderson, Global Blood Therapeutics; Dennis Schaffner, Sanofi-Genzyme; Edward Eldridge, Gilead; **Erica Finanger, OHSU*;** Gregg Rasmussen, Vertex; **Jaime Smutko, Global Blood Therapeutics*;** Jean Ritter, Zealand Pharma; Jeanne Vander Zaden, Biocodex MSL; Jenny Todenhagen, Genentech; Jill Johnson, Genentech; Kara Tyelr, Kite Pharma; Kelly Maynard, Little Hercules Foundation; Ken Orr, Global Blood Therapeutics; Kevin Black, SK Life Science; Kristen Kross, Sobi; Lance Swanson; Laura Jeffcoat, AbbVie; Lee Stout, Chiesei; LeeAnna Hoskins; **Lisa Allen, Vertex*; Lisa Borland, Sarepta Therapeutics***; Lynda Finch, Biogen; **Margaret Olmon, Abbvie***; Mark Kantor, AllCare; Matt Metcalf, Sobi; Timothy McFerron, Alkermes; Michael Foster, BMS; Michelle Bice, Gilead Sciences; Mike Donabedian, Sarepta; Nichole Roblin, Otsuka; Oyinda Osibanjo, YVFWC; Paul Genentech; Rick Frees, Vertex; Robb Host; **Robert Ahlstrom, PhD, Sobi*;** Roy Lindfield, Sunovion;

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Shari Yamada, Agios; Steve Hall Genentech; Steve Isaki, Lundbeck; **Stuart O'Brochta, Gilead***; Subrat Roychoudhary, Novartis; Tom Arnhart, UltragenRx; Tracy Copeland, Sarepta; Troy Pendergraft, IQVIA; Any Burns, AllCare; Carrie Johnson, PharmD, Amgen; Jeff Odell, UltragenRx; Jennifer Shear, Teva Pharmaceuticals, Mike Willet, Pfizer; Norm Navarro, Providence; Wendy Bibeau

(*) Provided verbal testimony

Written testimony: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff
B. Conflict of Interest Declaration - No new conflicts of interest were declared
C. Approval of February 2020 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor
D. Department Update provided by Dee Weston

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
B. P&T Annual Report
C. Acne Class Update w/ New Drug evaluation (NDE):
Make no changes to the PMPDP based on clinical evidenced; update the prior authorization (PA) criteria as proposed; and evaluate costs in executive session
D. Antiepileptics Class Update w/ NDE:
Designate Xcopri® (cenobamate) as non-preferred on the PMPDP based on clinical evidence and evaluate costs in executive session
E. Fluoroquinolones Drug Use Evaluation (DUE):
No policy changes were recommended at this time based on the DUE
F. Oral Diuretics Class Update:
Designate chlorthalidone as preferred on the PMPDP based on clinical evidence and evaluate costs in executive session
G. Orphan Drug Policy Update:
Add Crysvita® (burosumab-twza), Brineura® (cerliponase alfa), and Reblozyl® (luspatercept) to the Orphan Drugs PA criteria to support medically appropriate use based on their Food and Drug Administration (FDA) labeling

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

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III. DUR ACTIVITIES

A. ProDUR Report - Mr. Holsapple presented the ProDUR report
B. RetroDUR Report – Dr. Engen presented the RetroDUR Report
C. Oregon State Drug Reviews
   1. CGRP Antagonists in Migraine Prophylaxis
   2. Evidence for Drugs that are Heavily Marketed

   Dr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters

IV. DUR OLD BUSINESS

A. Oral Multiple Sclerosis Drugs
   Dr. Servid presented the proposed PA criteria updates:

   ACTION: The Committee recommended updating the Oral Multiple Sclerosis Drugs PA criteria to accommodate expanded FDA approved indications and to include all new fumarate salts. The Committee also approved removing Daclizumab from the Ocrelizumab PA criteria - as it has been voluntarily recalled from the U.S. market - and to modify the goals to clarify that primary progressive multiple sclerosis (PPMS) does not require step therapy
   Motion to approve, 2nd, all in favor

V. DUR NEW BUSINESS

A. Oncology Prior Authorization (PA) Policy Proposal
   Dr. Servid presented the policy proposal and proposed PA criteria:

   ACTION: The Committee recommended implementing the proposed Oncology Agents PA criteria and to apply to: all antineoplastic drugs originally approved by the FDA on 1/1/2008 or later; all new molecular entities and new formulations of antineoplastic drugs that already require PA; and all new FDA approved antineoplastic agents. The Committee will be notified of new drugs added to the policy at subsequent meetings
   Motion to approve, 2nd, all in favor

B. Hepatitis C, Direct-Acting Antivirals Policy Evaluation and Literature Scan
   Dr. McKenzie presented the Policy Evaluation and Dr. Herink presented the Literature Scan and proposed updates to the DAA PA criteria:

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ACTION: The Committee recommended amending the DAA PA criteria to include new FDA approved indications in pediatric patients and to remove the requirement for a pregnancy test. Case management was instead proposed to address risks associated with birth control and pregnancy. The Committee also recommended updating the Table of Recommended Treatment Regimens to accommodate any expanded or new FDA-indications for current recommended regimens and to add guidance for patients who have a contraindication or intolerance to ribavirin
Motion to approve, 2nd, all in favor

C. Dose Consolidation Policy Proposal
Dr. Fletcher presented the policy proposal:

ACTION: The Committee recommended implementing pharmacy point of sale (POS) edits to consolidate medications with fixed prices across various strengths, in conjunction with a safety net RetroDUR - including a form letter for pharmacies to notify providers when they make a change to the prescription
Motion to approve, 2nd, all in favor

VI. PREFERRED DRUG LIST NEW BUSINESS

A. Sickle Cell Disease (SCD) Class Review and New Drug Evaluation (NDE)
Dr. Sentena presented the proposal to:
1. Create a PMPDP class for the SCD drugs
2. Make a hydroxyurea formulation a preferred treatment
3. Designate Oxbryta™ (voxelotor) and Adakveo® (crizanlizumab-tmca) as non-preferred
4. Implement the proposed SCD PA criteria
5. Evaluate comparative costs in executive session

ACTION: The Committee amended to the proposed SCD PA criteria posted in the packet to also apply to L-glutamine.
Motion to approve, 2nd, all in favor

B. Drugs for Duchenne Muscular Dystrophy (DMD) Class Update w/ NDE
Dr. Servid presented the proposal to:
1. Update the DMD PA criteria to incorporate Vyondys 53® (golodirsen) as proposed

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

C. Idiopathic Pulmonary Fibrosis Class Update
Dr. Gibler presented the proposal to:
1. Update the PA criteria as proposed
2. Expand and rename the PMPDP class to cover approved indications for Interstitial Lung Disease - which includes idiopathic pulmonary fibrosis
3. Make no changes to the PMPDP based on the clinical evidence

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

D. Cystic Fibrosis Class Update with NDE
Dr. Herink presented the proposal to:
1. Maintain Trikafta™ (elexacaftor/tezacaftor/ivacaftor) as non-preferred and add to the Oral CF Modulators PA criteria as proposed
2. Update the PA criteria for initial approval of 6 months and 12 months for subsequent approval

ACTION: The Committee also recommended removing the required sweat chloride test from the renewal criteria for ivacaftor
Motion to approve, 2nd, all in favor

E. Laxatives for Chronic Constipation Class Update
Dr. Moretz presented the proposal to:
1. Revise the Drugs for Constipation PA criteria to include Motegrity™ (prucalopride), Zelnorm® (tegaserod), and Ibsrela® (tenapanor)
2. Designate all three non-preferred on the PMPDP to assure use for OHP funded conditions
3. Evaluate comparative costs in executive session

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

F. Gamifant™ (emapalumab-lzsg) New Drug Evaluation
Dr. Engen presented the proposal to:
1. Create a PMPDP class for the hemophagocytic lymphohistiocytosis (HLH) drugs
2. Designate Gamifant® (emapalumab-lzsg) as non-preferred
3. Implement the proposed Emapalumab PA criteria

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

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VII. EXECUTIVE SESSION

Members Present: Mark Helm, MD, MBA, FAAP; Caryn Mickelson, PharmD; Russell Huffman, DNP, PMHNP; Tracy Klein, PHD, FNP; William Origer, MD, James Slater, PharmD; Patrick DeMartino, MD, MPh; Stacy Ramirez, PharmD; Cathy Zehrung RPh; David Pass, MD

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Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston, JD; Brandon Wells; Jennifer Bowen

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Acne Class Update w/ New Drug evaluation (NDE):
Recommendation: make Altreno™ (tretinoin) and Arazlo™ (tazarotene) non-preferred and make unassigned benzoyl peroxide products preferred and subject to acne PA
ACTION: Motion to approve, 2nd, all in favor

B. Antiepileptics Class Update w/ NDE:
Recommendation: make no changes to the PMPDP

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

G. Oral Diuretics Class Update:
Recommendation: make chlorthalidone and generic triamterene/hydrochlorothiazide products preferred on the PMPDP

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

H. Sickle Cell Disease (SCD) Class Review and New Drug Evaluation (NDE)
Recommendation: make generic hydroxyurea capsules preferred and Droxia®, Hydrea®, Siklos®, and Endari™ (L-glutamine) non-preferred on the PMPDP

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

I. Laxatives for Chronic Constipation
Recommendation: make no changes to the PMPDP

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

IX. ADJOURN

X. OHA Rules Advisory Committee

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Pharmacy Utilization Summary Report: January 2019 - December 2019

Eligibility	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Total Members (FFS & Encounter)	970,009	973,211	979,795	981,514	979,468	979,316	980,226	981,629	983,778	985,585	983,689	987,294	980,460
FFS Members	118,919	119,390	125,420	113,342	112,672	115,232	91,378	99,920	100,302	93,871	98,749	99,972	107,431
OHP Basic with Medicare	33,066	33,109	33,374	28,706	29,057	29,456	8,912	9,279	9,365	9,067	9,362	9,174	20,161
OHP Basic without Medicare	11,916	11,789	11,811	11,739	11,877	12,010	11,793	11,967	12,047	11,869	12,431	12,040	11,941
ACA	73,937	74,492	80,235	72,897	71,738	73,766	70,673	78,674	78,890	72,935	76,956	78,758	75,329
Encounter Members	851,090	853,821	854,375	868,172	866,796	864,084	888,848	881,709	883,476	891,714	884,940	887,322	873,029
OHP Basic with Medicare	43,801	43,841	43,822	48,472	48,276	48,107	68,815	68,626	68,722	69,151	68,769	69,265	57,472
OHP Basic without Medicare	61,991	61,974	61,949	62,066	61,919	61,721	61,928	61,667	61,560	62,079	62,180	62,716	61,979
ACA	745,298	748,006	748,604	757,634	756,601	754,256	758,105	751,416	753,194	760,484	753,991	755,341	753,578

Gross Cost Figures for Drugs	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	YTD Sum
Total Amount Paid (FFS & Encounter)	$80,839,098	$72,614,166	$79,851,519	$84,116,986	$85,446,418	$77,696,490	$84,494,522	$82,620,058	$78,859,146	$87,431,159	$77,887,699	$84,125,402	$975,982,664
Mental Health Carve-Out Drugs	$8,178,165	$7,371,472	$7,872,599	$8,446,985	$8,552,787	$7,895,379	$8,777,722	$8,638,326	$8,059,207	$8,948,916	$8,129,248	$9,213,384	$100,084,193
OHP Basic with Medicare	$8,243	$6,573	$5,197	$5,313	$9,126	$19,504	$33,196	$41,678	$32,600	$39,134	$33,985	$42,387	$276,936
OHP Basic without Medicare	$3,308,623	$2,985,088	$3,108,303	$3,368,773	$3,391,645	$3,117,867	$3,477,151	$3,407,632	$3,100,210	$3,530,998	$3,193,246	$3,764,636	$39,754,171
ACA	$4,798,666	$4,314,731	$4,693,375	$5,008,046	$5,089,701	$4,709,249	$5,217,003	$5,138,577	$4,883,968	$5,331,548	$4,859,360	$5,349,822	$59,394,047
FFS Physical Health Drugs	$3,149,906	$2,628,499	$2,862,405	$2,880,401	$2,931,984	$2,724,631	$2,763,229	$2,709,262	$2,477,821	$2,916,655	$2,568,487	$2,787,608	$33,400,888
OHP Basic with Medicare	$255,779	$220,107	$258,327	$252,483	$213,753	$191,626	$49,634	$50,568	$50,689	$60,397	$52,237	$60,831	$1,716,431
OHP Basic without Medicare	$1,027,448	$877,313	$948,305	$914,468	$976,791	$993,415	$1,091,302	$978,132	$864,959	$1,098,333	$868,256	$971,850	$11,610,572
ACA	$1,744,092	$1,418,666	$1,541,019	$1,579,942	$1,598,336	$1,436,382	$1,522,891	$1,534,466	$1,429,855	$1,598,525	$1,521,433	$1,620,421	$18,546,031
FFS Physician Administered Drugs	$1,913,421	$1,951,965	$1,746,947	$1,449,855	$1,523,542	$1,865,268	$1,160,036	$1,266,669	$1,470,537	$1,417,804	$1,249,706	$1,015,509	$18,031,257
OHP Basic with Medicare	$553,771	$488,923	$488,053	$366,652	$387,515	$338,635	$123,043	$173,190	$170,781	$145,192	$129,884	$92,937	$3,458,576
OHP Basic without Medicare	$330,128	$519,485	$234,762	$248,746	$242,006	$571,302	$190,321	$158,924	$570,408	$406,573	$367,480	$190,430	$4,030,565
ACA	$615,074	$559,700	$570,226	$418,087	$466,924	$563,618	$355,439	$513,284	$401,363	$391,789	$422,419	$443,827	$5,721,751
Encounter Physical Health Drugs	$53,581,648	$48,788,447	$54,689,774	$57,524,199	$58,003,397	$52,050,436	$56,702,939	$55,832,021	$53,799,472	$59,479,606	$53,085,805	$56,835,621	$660,373,365
OHP Basic with Medicare	$320,730	$267,085	$308,011	$300,078	$360,505	$566,605	$771,894	$714,615	$732,856	$819,273	$757,046	$713,998	$6,632,697
OHP Basic without Medicare	$13,549,627	$11,987,408	$13,363,412	$14,411,598	$14,591,529	$13,246,561	$13,894,327	$13,435,314	$12,771,931	$14,341,615	$13,213,495	$14,164,779	$162,971,597
ACA	$38,940,104	$35,843,494	$40,347,513	$42,138,222	$42,410,916	$37,648,661	$41,395,526	$41,089,273	$39,679,718	$43,714,727	$38,592,282	$41,301,073	$483,101,510
Encounter Physician Administered Drugs	$14,015,958	$11,873,783	$12,679,793	$13,815,546	$14,434,709	$13,160,776	$15,090,596	$14,173,781	$13,052,108	$14,668,177	$12,854,453	$14,273,279	$164,092,960
OHP Basic with Medicare	$403,789	$313,078	$280,250	$323,388	$373,931	$320,759	$532,313	$490,976	$532,639	$571,953	$536,651	$539,998	$5,219,726
OHP Basic without Medicare	$3,077,014	$2,924,647	$2,850,739	$3,085,393	$3,388,698	$2,852,486	$2,877,336	$2,962,351	$2,684,917	$3,166,656	$2,595,890	$3,055,966	$35,522,095
ACA	$10,349,665	$8,502,746	$9,382,109	$10,198,439	$10,469,469	$9,833,104	$11,256,115	$10,397,651	$9,528,653	$10,620,706	$9,276,757	$10,171,314	$119,986,726

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: July 23, 2020

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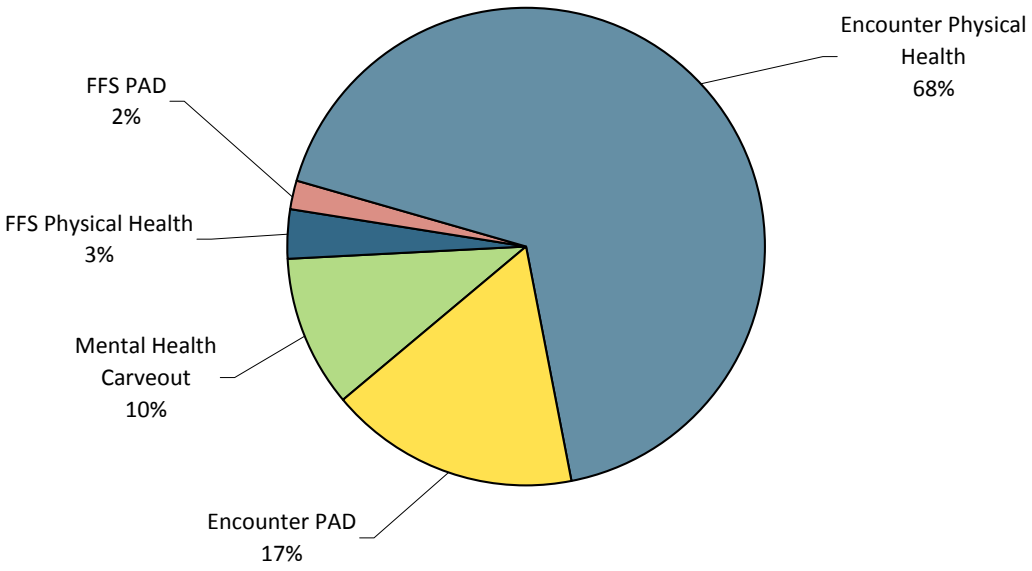
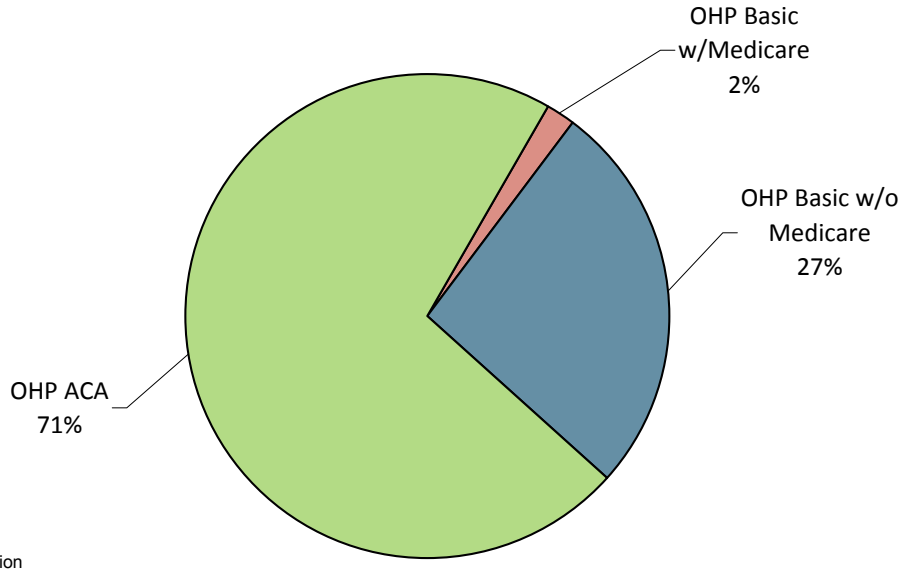
YTD Percent Paid Amounts





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

Last Updated: July 23, 2020

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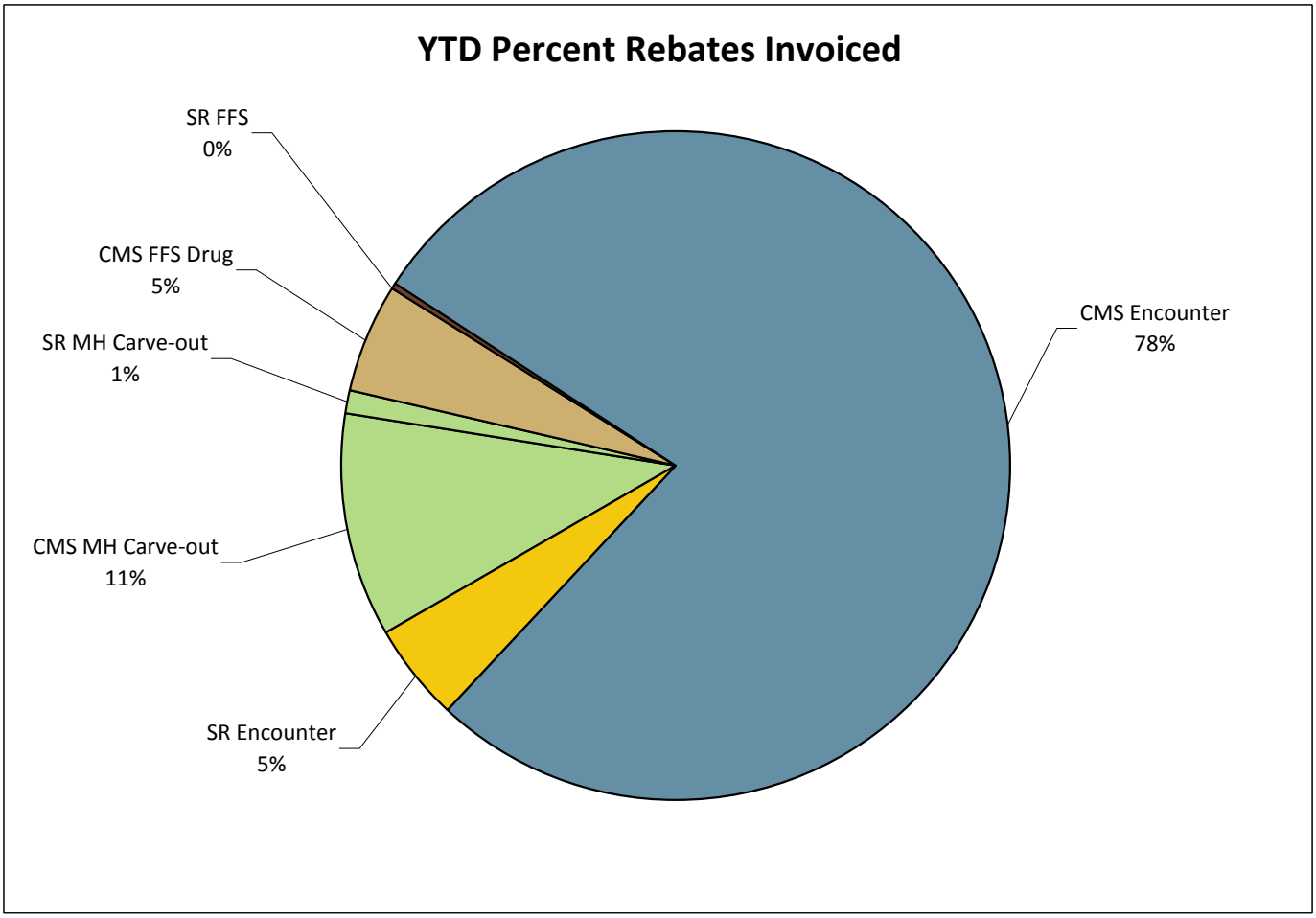
Pharmacy Utilization Summary Report: January 2019 - December 2019

Quarterly Rebates Invoiced	2019-Q1	2019-Q2	2019-Q3	2019-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$102,109,982	$106,357,113	$105,187,724	$105,076,508	$418,731,326
CMS MH Carve-out	$11,132,578	$11,402,626	$11,213,750	$11,474,193	$45,223,147
SR MH Carve-out	$1,065,433	$1,120,134	$1,156,887	$1,270,415	$4,612,869
CMS FFS Drug	$6,286,819	$6,011,696	$5,085,389	$5,001,001	$22,384,904
SR FFS	$248,013	$305,606	$301,351	$329,386	$1,184,357
CMS Encounter	$79,503,443	$81,475,522	$82,678,320	$81,962,158	$325,619,443
SR Encounter	$3,873,696	$6,041,528	$4,752,028	$5,039,354	$19,706,607

Quaterly Net Drug Costs	2019-Q1	2019-Q2	2019-Q3	2019-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$131,194,801	$140,902,781	$140,786,002	$144,367,752	$557,251,338
Mental Health Carve-Out Drugs	$11,224,225	$12,372,390	$13,104,619	$13,546,942	$50,248,177
FFS Phys Health + PAD	$7,718,311	$7,058,378	$6,460,814	$6,625,382	$27,862,885
Encounter Phys Health + PAD	$112,252,265	$121,472,013	$121,220,569	$124,195,429	$479,140,276



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

Last Updated: July 23, 2020

Drug Use Research & Management Program
DHS - Health Systems Division
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Pharmacy Utilization Summary Report: January 2019 - December 2019

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$83.34	$74.61	$81.50	$85.70	$87.24	$79.34	$86.20	$84.17	$80.16	$88.71	$79.18	$85.21	$82.95
Mental Health Carve-Out Drugs	$8.43	$7.57	$8.03	$8.61	$8.73	$8.06	$8.95	$8.80	$8.19	$9.08	$8.26	$9.33	$8.51
FFS Physical Health Drugs	$26.49	$22.02	$22.82	$25.41	$26.02	$23.64	$30.24	$27.11	$24.70	$31.07	$26.01	$27.88	$26.12
FFS Physician Administered Drugs	$16.09	$16.35	$13.93	$12.79	$13.52	$16.19	$12.69	$12.68	$14.66	$15.10	$12.66	$10.16	$13.90
Encounter Physical Health Drugs	$62.96	$57.14	$64.01	$66.26	$66.92	$60.24	$63.79	$63.32	$60.90	$66.70	$59.99	$64.05	$63.02
Encounter Physician Administered Drugs	$16.47	$13.91	$14.84	$15.91	$16.65	$15.23	$16.98	$16.08	$14.77	$16.45	$14.53	$16.09	$15.66

Claim Counts	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Total Claim Count (FFS & Encounter)	1,083,474	965,136	1,055,902	1,076,880	1,087,552	1,003,889	1,070,596	1,049,485	1,027,867	1,104,083	1,005,697	1,078,142	1,050,725
Mental Health Carve-Out Drugs	163,393	145,281	156,633	162,563	163,452	151,526	165,148	161,553	156,881	167,838	154,105	166,066	159,537
FFS Physical Health Drugs	60,182	53,707	58,698	56,939	56,909	51,210	43,105	42,362	41,649	43,809	39,754	42,864	49,266
FFS Physician Administered Drugs	16,074	13,275	14,837	13,951	14,674	13,374	12,395	11,971	11,354	11,697	9,933	9,700	12,770
Encounter Physical Health Drugs	729,477	651,244	713,187	727,519	734,362	676,145	725,929	708,004	698,115	755,313	683,316	734,576	711,432
Encounter Physician Administered Drugs	114,348	101,629	112,547	115,908	118,155	111,634	124,019	125,595	119,868	125,426	118,589	124,936	117,721

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$74.61	$75.24	$75.62	$78.11	$78.57	$77.40	$78.92	$78.72	$76.72	$79.19	$77.45	$78.03	$77.38
Mental Health Carve-Out Drugs	$50.05	$50.74	$50.26	$51.96	$52.33	$52.11	$53.15	$53.47	$51.37	$53.32	$52.75	$55.48	$52.25
FFS Physical Health Drugs	$52.34	$48.94	$48.76	$50.59	$51.52	$53.21	$64.10	$63.96	$59.49	$66.58	$64.61	$65.03	$57.43
FFS Physician Administered Drugs	$119.04	$147.04	$117.74	$103.92	$103.83	$139.47	$93.59	$105.81	$129.52	$121.21	$125.81	$104.69	$117.64
Encounter Physical Health Drugs	$73.45	$74.92	$76.68	$79.07	$78.98	$76.98	$78.11	$78.86	$77.06	$78.75	$77.69	$77.37	$77.33
Encounter Physician Administered Drugs	$122.57	$116.83	$112.66	$119.19	$122.17	$117.89	$121.68	$112.85	$108.89	$116.95	$108.39	$114.24	$116.19

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$18.30	$19.43	$19.56	$18.77	$18.88	$18.75	$19.19	$19.35	$19.25	$19.47	$18.83	$19.13	$19.08
Mental Health Carve-Out Drugs	$18.03	$18.17	$17.49	$17.96	$18.15	$18.24	$18.40	$18.21	$17.41	$17.52	$17.58	$18.07	$17.94
FFS Physical Health Drugs	$16.65	$16.87	$17.48	$17.95	$17.18	$17.60	$19.10	$19.77	$19.18	$21.33	$20.61	$20.52	$18.69
Encounter Physical Health Drugs	$18.49	$19.94	$20.23	$19.02	$19.18	$18.96	$19.39	$19.61	$19.71	$19.85	$19.04	$19.32	$19.40

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$365.68	$404.62	$448.23	$478.84	$484.77	$476.69	$494.66	$503.37	$466.83	$468.81	$488.04	$498.92	$464.96
Mental Health Carve-Out Drugs	$1,031.75	$1,041.57	$1,045.58	$1,068.47	$1,064.21	$1,063.93	$1,078.40	$1,073.22	$1,048.35	$1,074.08	$1,059.63	$1,059.15	$1,059.03
FFS Physical Health Drugs	$161.43	$153.09	$161.56	$170.60	$179.67	$190.54	$261.49	$261.99	$232.49	$256.99	$258.10	$252.14	$211.67
Encounter Physical Health Drugs	$362.19	$407.18	$455.48	$485.78	$490.94	$478.26	$480.66	$489.79	$454.24	$452.65	$473.52	$484.63	$459.61

Generic Drug Use Percentage	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Generic Drug Use Percentage	85.7%	87.1%	88.1%	88.3%	88.4%	88.5%	88.7%	88.8%	88.3%	87.9%	88.5%	88.8%	88.1%
Mental Health Carve-Out Drugs	96.8%	96.8%	96.8%	96.8%	96.7%	96.8%	96.7%	96.7%	96.7%	96.6%	96.6%	96.4%	96.7%
FFS Physical Health Drugs	75.3%	76.5%	78.3%	78.6%	78.9%	79.4%	81.4%	81.8%	81.1%	80.8%	81.5%	80.8%	79.5%
Encounter Physical Health Drugs	84.0%	85.8%	87.0%	87.1%	87.3%	87.4%	87.3%	87.4%	86.8%	86.4%	87.1%	87.5%	86.8%

Preferred Drug Use Percentage	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Avg Monthly
Preferred Drug Use Percentage	85.82%	85.73%	85.72%	85.54%	85.52%	85.46%	85.42%	85.34%	85.26%	85.05%	85.43%	85.47%	85.5%
Mental Health Carve-Out Drugs	74.13%	73.91%	73.65%	73.66%	73.51%	73.26%	73.18%	73.18%	73.23%	73.31%	73.11%	72.92%	73.4%
FFS Physical Health Drugs	95.50%	95.43%	95.52%	95.23%	95.24%	95.48%	94.50%	94.58%	94.58%	94.56%	94.68%	94.89%	95.0%
Encounter Physical Health Drugs	87.66%	87.59%	87.59%	87.47%	87.47%	87.46%	87.65%	87.56%	87.43%	87.15%	87.71%	87.78%	87.5%

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: July 23, 2020

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2020

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,191,606	16.4%	5,036	$1,229	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,899,926	7.7%	1,430	$2,028	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,126,941	5.6%	1,882	$1,130	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,530,828	4.1%	771	$1,986	Y
5	REXULTI	Antipsychotics, 2nd Gen	$1,453,733	3.9%	1,330	$1,093	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$733,424	1.9%	118	$6,215	Y
7	ARISTADA	Antipsychotics, Parenteral	$576,820	1.5%	254	$2,271	Y
8	TRINTELLIX	Antidepressants	$569,512	1.5%	1,441	$395	V
9	SAPHRIS	Antipsychotics, 2nd Gen	$505,410	1.3%	702	$720	Y
10	BUPROPION XL	Antidepressants	$488,246	1.3%	27,346	$18	V
11	SERTRALINE HCL	Antidepressants	$472,961	1.3%	45,532	$10	Y
12	VIIBRYD	Antidepressants	$443,625	1.2%	1,514	$293	V
13	DULOXETINE HCL	Antidepressants	$436,235	1.2%	30,298	$14	V
14	TRAZODONE HCL	Antidepressants	$426,453	1.1%	42,281	$10	
15	FLUOXETINE HCL	Antidepressants	$419,614	1.1%	33,383	$13	Y
16	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$348,493	0.9%	1,804	$193	V
17	ATOMOXETINE HCL*	ADHD Drugs	$303,852	0.8%	5,149	$59	Y
18	VENLAFAXINE HCL ER	Antidepressants	$303,305	0.8%	1,870	$162	V
19	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$286,694	0.8%	20,864	$14	
20	ESCITALOPRAM OXALATE	Antidepressants	$285,069	0.8%	27,885	$10	Y
21	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$282,245	0.7%	313	$902	Y
22	LATUDA	Antipsychotics, 2nd Gen	$267,042	0.7%	228	$1,171	
23	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$266,053	0.7%	24	$11,086	Y
24	BIKTARVY	HIV	$259,339	0.7%	96	$2,701	Y
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	$255,377	0.7%	23,660	$11	Y
26	CHOLBAM*	Bile Therapy	$248,996	0.7%	6	$41,499	N
27	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$240,393	0.6%	15,393	$16	V
28	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$224,170	0.6%	2,123	$106	V
29	TRIKAFTA*	Cystic Fibrosis	$215,373	0.6%	21	$10,256	N
30	CONCERTA*	ADHD Drugs	$203,279	0.5%	697	$292	N
31	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$199,058	0.5%	16,907	$12	Y
32	AMITRIPTYLINE HCL*	Antidepressants	$195,734	0.5%	13,668	$14	Y
33	VENLAFAXINE HCL ER	Antidepressants	$192,378	0.5%	14,996	$13	Y
34	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$185,153	0.5%	39	$4,748	Y
35	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$181,181	0.5%	6	$30,197	
36	CITALOPRAM HBR	Antidepressants	$177,020	0.5%	19,959	$9	Y
37	Inj Pembrolizumab	Physican Administered Drug	$176,038	0.5%	47	$3,745	
38	LANTUS SOLOSTAR*	Diabetes, Insulins	$158,918	0.4%	404	$393	Y
39	MIRTAZAPINE	Antidepressants	$146,752	0.4%	9,223	$16	Y
40	FETZIMA	Antidepressants	$143,717	0.4%	349	$412	V
		Top 40 Aggregate:	**$25,020,963**		**369,049**	**$3,137**	
		All FFS Drugs Totals:	**$37,719,073**		**640,769**	**$392**	

*** 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: July 23, 2020

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2020

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$267,042	2.3%	228	$1,171	
2	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$266,053	2.3%	24	$11,086	Y
3	BIKTARVY	HIV	$259,339	2.3%	96	$2,701	Y
4	CHOLBAM*	Bile Therapy	$248,996	2.2%	6	$41,499	N
5	TRIKAFTA*	Cystic Fibrosis	$215,373	1.9%	21	$10,256	N
6	CONCERTA*	ADHD Drugs	$203,279	1.8%	697	$292	N
7	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$185,153	1.6%	39	$4,748	Y
8	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$181,181	1.6%	6	$30,197	
9	Inj Pembrolizumab	Physican Administered Drug	$176,038	1.5%	47	$3,745	
10	LANTUS SOLOSTAR*	Diabetes, Insulins	$158,918	1.4%	404	$393	Y
11	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$139,833	1.2%	583	$240	
12	PROMACTA	Thrombocytopenia Drugs	$132,806	1.2%	10	$13,281	Y
13	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$123,144	1.1%	11	$11,195	
14	Factor Viii Pegylated Recomb	Physican Administered Drug	$123,135	1.1%	4	$30,784	
15	INVEGA SUSTENNA	Antipsychotics, Parenteral	$122,766	1.1%	58	$2,117	
16	VYVANSE*	ADHD Drugs	$105,327	0.9%	655	$161	Y
17	VRAYLAR	Antipsychotics, 2nd Gen	$100,605	0.9%	91	$1,106	
18	Etonogestrel Implant System	Physican Administered Drug	$99,589	0.9%	139	$716	
19	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$99,189	0.9%	2,497	$40	Y
20	ELIQUIS	Anticoagulants, Oral and SQ	$96,645	0.8%	286	$338	Y
21	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$94,647	0.8%	1,577	$60	Y
22	NOVOLOG FLEXPEN	Diabetes, Insulins	$90,950	0.8%	152	$598	Y
23	FLOVENT HFA	Corticosteroids, Inhaled	$90,467	0.8%	537	$168	Y
24	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$89,867	0.8%	30	$2,996	Y
25	REXULTI	Antipsychotics, 2nd Gen	$84,014	0.7%	77	$1,091	
26	VIMPAT	Antiepileptics (oral & rectal)	$82,912	0.7%	202	$410	Y
27	TRUVADA	HIV	$82,133	0.7%	61	$1,346	Y
28	Aflibercept Injection	Physican Administered Drug	$81,029	0.7%	165	$491	
29	XULANE	STC 63 - Oral Contraceptives	$78,282	0.7%	449	$174	
30	LEVEMIR FLEXTOUCH	Diabetes, Insulins	$77,890	0.7%	139	$560	Y
31	ADVATE	Antihemophilia Factors	$75,383	0.7%	4	$18,846	
32	VIGABATRIN	Antiepileptics (oral & rectal)	$74,133	0.6%	7	$10,590	N
33	Inj., Durvalumab, 10 Mg	Physican Administered Drug	$70,815	0.6%	49	$1,445	
34	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$70,671	0.6%	7	$10,096	N
35	STELARA*	Biologics for Autoimmune Conditions	$69,329	0.6%	12	$5,777	N
36	LANTUS	Diabetes, Insulins	$68,680	0.6%	205	$335	Y
37	IBRANCE*	Antineoplastics, Newer	$62,298	0.5%	5	$12,460	
38	CIMZIA*	Biologics for Autoimmune Conditions	$61,970	0.5%	17	$3,645	N
39	Mirena, 52 Mg	Physican Administered Drug	$60,705	0.5%	101	$601	
40	SPIRIVA	Anticholinergics, Inhaled	$60,314	0.5%	149	$405	Y
		Top 40 Aggregate:	**$4,830,896**		**9,847**	**$5,954**	
		All FFS Drugs Totals:	**$11,447,891**		**159,630**	**$391**	

*** 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: July 23, 2020

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Drug Class Update with New Drug Evaluation: Antipsychotics

Date of Review: August 2020

Date of Last Review: March 2019
Dates of Literature Search: 01/01/2019 - 03/12/2020
Brand Name (Manufacturer): Caplyta® (Intra-Cellular Therapeutics, Inc)
Dossier Received: yes

Generic Name: Lumateperone

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

Purpose for Class Update:
Evidence for the comparative effectiveness of first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and parenteral antipsychotic products was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in March 2019. This review examines recently published comparative evidence of FGA, SGA, and parenteral antipsychotics, as well as to the efficacy and safety of lumateperone, a SGA which received Food and Drug Administration (FDA) approval in 2019.

Research Questions:
1. Is there new comparative evidence of meaningful difference in clinical efficacy or effectiveness between oral FGAs or SGAs, or between oral antipsychotic agents and parenteral antipsychotic agents (first- or second-generation) for schizophrenia, bipolar mania, or major depressive disorder?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or compared to parenteral antipsychotic agents?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics (age, gender, or comorbidities), treatment history (treatment naive or treatment resistant), or concomitant medications?
4. What is the evidence for efficacy and safety with lumateperone?

Conclusions:
- No systematic reviews were included in this class update.
- A 2019 guideline by the American Academy of Neurology on Tourette syndrome (TS) and chronic tic disorders included recommendations for antipsychotic drugs (APD) for tics when the benefit outweighs the risk (level C).[1,2] Haloperidol, risperidone, aripiprazole, and tiapride are *probably* more likely than placebo to reduce tic severity, while pimozide, ziprasidone, and metoclopramide *possibly* reduce tic severity when compared to placebo.[1,2] Insufficient evidence of comparative efficacy between these medications is available.[1,2]

Author: Sara Fletcher, PharmD, MPH, BCPS

- There is low quality evidence that lumateperone 42 mg once daily may reduce Positive and Negative Syndrome Scale (PANSS) score from baseline compared to placebo in two similarly designed trials [least squares mean (LSM) -13.4 vs. -7.4, p=0.017[3] and LSM -14.5 vs. -10.3, p=0.02[4]] after 4 weeks, though not after 6 weeks in a third trial (LSM -14.6 vs. -15.1, 95% confidence interval (CI) -2.9 to 3.8[5]), in patients with schizophrenia who are not treatment-naïve or treatment-resistant. Patients and endpoints were extremely similar across the three studies. Evidence is limited by attrition bias, reporting bias, funding bias, and inconsistency of efficacy results and dose-response with lack of benefit in at least one trial with every dosage strength studied.[3-5]
- There is no evidence that other doses of lumateperone (14 mg, 28 mg, 84 mg) are superior to placebo in reducing PANSS score over 4-6 weeks due to lack of statistical significance when studied.[3-5]
- There is insufficient evidence to determine if lumateperone offers superior efficacy or safety compared to any other APD for schizophrenia.[3-5]
- There is no new evidence assessing safety and harms between various APD products. Warnings were added to the clozapine labeling that untreated constipation can lead to serious bowel problems.[6]

Recommendations:
- No further review or research needed at this time.
- No changes to the preferred drug list (PDL) are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
In the Oregon Health Plan, APDs are exempt from traditional PDL and PA requirements. However, clinical PA criteria that address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use, and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The PA criteria for these safety edits are outlined in **Appendix 5**. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone palmitate, and risperidone are on the PDL. Oral APDs on the PDL include chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, and risperidone. Most APD use in the Oregon Medicaid population is for oral SGAs, including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of APD claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable APDs in this class. The APDs included on the Oregon PDL are presented in **Appendix 1**.

Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania, or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high quality systematic reviews to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other APDs.

Background:
Antipsychotic medications are typically categorized as FGAs and SGAs. **Appendix 1** lists the oral and parenteral FGAs and SGAs which are currently available. Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[7] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression, and nausea or vomiting.[7]

Schizophrenia is characterized by presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of at least 2 of these symptoms (one must be either delusions, hallucinations or disorganized speech) for longer than 6 months. Symptoms are commonly categorized as positive symptoms (delusions and hallucinations) or negative symptoms (blunted affect, alogia, asociality, anhedonia, and avolition).[8] Onset of schizophrenia occurs most commonly in early adulthood and can have a significant impact on quality of life. Approximately 20% of patients remain relapse-free after a first psychotic episode.[9] However, the majority of patients experience relapse or continued symptoms which can decrease quality of life and create social or occupational difficulties. Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, and slow or early disease onset at less than 18 years of age.[9] Schizophrenia has been associated with increased risk of mortality, and is often also associated with increased cannabis use, substance abuse, and higher rates of depression.[9] Treatment indicated for schizophrenia includes both FGAs and SGAs. First-generation antipsychotics are generally associated with higher incidence of extrapyramidal side effects whereas SGAs may have increased risk for long-term cardiovascular adverse effects.[9] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also often combined with pharmacological therapy.[9] Initial medication selection is often dependent on effectiveness and risks for adverse effects.

Bipolar disorder is characterized by episodes of mania and episodes of depression or hypomania and is estimated to occur in approximately 2% of the world population.[10] Initial diagnosis is most common in patients less than 25 years of age.[10] It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes, but without manic episodes).[10] It can be further classified as rapid cycling with at least 4 episodes of mania, hypomania or depression per year, mania with mixed features, or mania with psychotic features (including hallucinations or delusions).[10] Frequently bipolar disorder is associated with other mental health conditions including anxiety disorder, ADHD and substance use disorders.[10] First-line treatment for bipolar disorder is medication therapy including APDs or mood stabilizers such as lithium, divalproex, quetiapine, or lamotrigine.[10] Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[11] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[10] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy. The American Psychiatric Association and the National Institute for Health and Clinical Excellence (NICE) recommends ECT as an option for patients with life-threatening suicidality, psychosis or refusal to eat.[10] ECT may also be considered with severe or treatment-resistant bipolar depression and as a first-line option for pregnant women with severe depression.[10]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7-point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference (MCID).[8,11] The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in patients with schizophrenia each scored on a 7-point scale with lower scores indicating less severe symptoms (range 30-210). This scale can also be sub-divided to assess general psychopathology, positive symptoms, or negative symptoms. Response to treatment is typically defined as greater than 20% improvement in the PANSS score, though this definition can vary among trials.[9,12] There is no established MCID for the PANSS, though improvements of 4-8 points have been correlated to increases in employment and improvements of 10 points have been correlated with reduced hospitalization. Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Each item is assessed on a 0-5 point scale with higher scores indicating more severe symptoms (range 0-125). The Brief Psychiatric Rating Scale (BPRS) assesses schizophrenia symptom severity via assessment of 16-18 items (each assessed on a 7-point scale with a total score of 0 to 126). Similarly, quality of life and functional improvement may be assessed using a variety of metrics. The Global Assessment Scale of

Functioning (GAF) scale is commonly used for patients with schizophrenia and assesses functional improvement on a 0 to 100 scale. Clinically important improvements in function have been correlated to changes of at least 10 points.[9]

For patients with bipolar disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[11,13] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a MCID of 1 point).[11]

Most APD use is for SGAs, with over 25,000 patients with claims for them each quarter. Approximately 1500 and 1200 patients have prescriptions for FGAs and parenteral antipsychotics filled quarterly.

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

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

Systematic Reviews:
After review, 33 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[14-31] wrong study design of included trials (e.g., observational),[32-38] comparator (e.g., no control or placebo-controlled),[39,40] or outcome studied (e.g., non-clinical).[41-46]

New Guidelines:
High Quality Guidelines:
Tourette Syndrome and Chronic Tic Disorders: American Academy of Neurology
The American Academy of Neurology published a 2019 guideline of recommendations on the management of tics in people with TS and chronic tic disorders.[1]
The authors included a systematic review and evidence quality assessment to answer the following questions:

- In children and adults with TS or a chronic tic disorder, when should clinicians and patients pursue treatment for tics?
- In children and adults with TS or a chronic tic disorder who require treatment for tics, how should clinicians and patients choose between evidence-based treatment options and determine the sequence or combinations of these treatments?

These guidelines include 46 recommendations related to the assessment and management of TS and chronic tic disorders. A systematic literature review with evidence quality and risk of bias grading was conducted. The research team excluded those with conflicts of interest (COI) from decision making and the chairperson was free of all COI. Due to the paucity of data in some areas related to this condition, there was a need for extensive expert opinion where data were lacking. Four different premises were used in the development of the recommendations based upon availability of evidence and usage of expert opinion in

the absence of direct data. These include: (1) evidence-based conclusions from systematic review, (2) generally accepted principles of care, (3) strong evidence from related conditions, and (4) deductive inferences from other premises.[1] When an evidence-based premise is used, the panel used A (must), B (should), and C (may) as recommendation designations based on the quality and magnitude of the evidence available.[1,2] All medication treatment recommendations were based on evidence and not premises 2 through 4 above. The details of the literature evaluation are published separately from the guidelines.[1,2]

Recommendations included in the guideline were:

- Clinicians may prescribe antipsychotics for tics when the benefit outweighs the risk (C).[1]
- Appropriate counseling and monitoring for side effects, including weight gain, metabolic changes, and extrapyramidal movements, must be done (A), and the lowest effective dose used (B).[1]
- Pimozide and ziprasidone and medications added to other QT prolonging agents must have a baseline electrocardiogram (A).[1]
- When medications are discontinued they should be tapered over weeks to months to avoid dyskinesias (B).[1] This recommendation is based on the assessment that haloperidol, risperidone, aripiprazole, and tiapride are probably more likely than placebo to reduce tic severity, while pimozide, ziprasidone, and metoclopramide possibly reduce tic severity when compared to placebo.[1]
- Insufficient evidence of comparative efficacy between these medications is available.[1]

After review, one guideline was excluded due to poor quality.[47]

New Formulations or Indications:
There were no new formulations or indications.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Clozapine	Clozaril®	1/28/2020	Warnings	Untreated constipation can lead to serious bowel problems. Evaluate bowel function and avoid concomitant use of agents such as anticholinergics which may cause gastrointestinal hypomotility.[6]

Randomized Controlled Trials:
A total of 54 citations were manually reviewed from the initial literature search and were excluded because of wrong study design (e.g., observational),[48-74] comparator (e.g., no control or placebo-controlled),[75-87] or outcome studied (e.g., non-clinical).[88-101]

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

Clinical Efficacy:
Lumateperone is a SGA antipsychotic indicated for the treatment of adult patients with schizophrenia at a dose of 42 mg once daily, without titration.[102] The exact mechanism of action is unclear. Lumateperone exhibits high affinity for serotonin 5-HT_{2A} receptors and moderate affinity for dopamine D_2 receptors.[102] Additionally, it has moderate affinity for serotonin transporters, dopamine D_1 and D_4 receptors, and adrenergic $alpha_{1A}$ and $alpha_{1B}$ receptors.[102] It has low affinity for muscarinic and histaminergic receptors.[102] Lumateperone has been studied in 3 applicable clinical trials, 2 of which are detailed in Table 4, while the remaining 1 failed to meet the primary endpoint and remains unpublished.[5]

Lumateperone tosylate was evaluated in a randomized, double-blind, placebo- and active- controlled, phase 2, multicenter trial conducted in the US (NCT 01499563).[3] Patients were randomized 1:1:1:1 to placebo, lumateperone tosylate 60 mg once daily (equivalent to lumateperone 42 mg), lumateperone tosylate 120 mg once daily (equivalent to lumateperone 84 mg), and risperidone 4 mg once daily.[3] There was a washout period of up to 7 days prior to randomization, followed by the assigned treatment for 28 days while the patient was inpatient.[3] Following this, patients were discontinued from study medication and stabilized on non-study APDs for 5 days and then discharged with follow-up 2 weeks after the last study dose for a safety assessment.[3] Included patients were 18-55 years of age with a DSM-Clinical Trials Version (DSM-CTV) diagnosis of schizophrenia and were experiencing an acute exacerbation of psychosis that began within the previous 4 weeks (defined as having a score of at least 40 using the 18-item Brief Psychiatric Rate Scale, with a score of at least 4 (range 1-7) on at least 2 positive symptom items of that scale).[3] Participants were required to have shown response to previous APD therapy.[3] Additional criteria are listed in Table 4. Patients were assessed at baseline and weekly using the PANSS by remote central raters who were trained to demonstrate high interrater reliability and who were blinded to study design, treatment, and time point of assessment.[3] Calgary Depression Scale for Schizophrenia (CDSS) was used to assess for depression while numerous other indicators and tools were used for the safety assessment; these were used by site-based raters after standardized training across study locations was conducted.[3]

The resulting study population was primarily male (82.6%) and African-American (78.1%), with a mean age 40.1 years.[3] The mean number of years since diagnosis ranged from 15.2 to 17.0 between treatment arms, while the mean baseline PANSS ranged from 84.6 to 88.1.[3] The primary efficacy endpoint, conducted on the modified intent-to-treat (mITT) population (those with a valid baseline and minimum of one post-dose assessment), was the change from baseline to day 28 of PANSS score versus placebo.[3] Statistical improvement from baseline when compared to placebo [LSM -7.4 $\pm$ standard error of the mean (SEM) 1.68] were lumateperone tosylate 60 mg (LSM -13.2 $\pm$ SEM 1.69; p=0.017), lumateperone tosylate 120 mg (LSM -8.3 $\pm$ SEM 1.68; p=0.708), and risperidone 4 mg (LSM -13.4 $\pm$ SEM 1.72; p=0.013).[3] The investigators could not explain why the lumateperone tosylate 120 mg dose did not show benefit when lumateperone tosylate 60 mg demonstrated a statistically significant benefit versus placebo, though higher rates of somnolence and sedation may have introduced detection bias by affecting behavior and masking therapeutic effects during centralized assessment. A sensitivity analysis was performed using the last observation carried forward, adjusted for baseline PANSS score, which again showed statistical significance only for lumateperone tosylate 60 mg [LS mean -12.3; SEM $\pm$ 1.7; p=0.011; effect size (ES)=0.41] and risperidone 4 mg (LS mean -12.6; SEM $\pm$ 1.7; p=0.008; ES=0.43), while lumateperone tosylate 120 mg was not statistically significantly different compared to placebo (LS mean -7.7; SEM $\pm$ 1.6; p=0.558; ES=0.09).[3] An a priori responder analysis of patients who had a reduction of at least 30% of the total PANSS score indicated 40.8% of patients taking lumateperone tosylate 60 mg (LSM 18.3%, 95% CI 3.9 to 32.6; p=0.014), 25.0% of patients taking lumateperone tosylate 120 mg (LSM 2.5%, 95% CI -10.7 to 15.7; p=0.711), and 40.0% of patients taking risperidone 4 mg (LSM 17.5%, 95% CI 3.1 to 31.9; p=0.019) were responders when compared to 22.5% for placebo.[3] Additionally, there were secondary a priori subgroup analyses of patients with negative symptoms and/or depression at baseline based on their PANSS or CDSS (Table 4).[3] The PANSS depression subgroup showed a statistically significant mean change of -31.7 (± 7.31 SEM; p=0.018) for lumateperone tosylate 60 mg versus placebo (mean change -12.4 ± 3.89 SEM).[3] The other study

groups were non-significant for this sub-group analysis, and no group was statistically different from placebo from analysis of the PANSS negative subscale subgroup.[3]

A second, similarly designed placebo-controlled study (NCT2282761) evaluated lumateperone 42 mg and lumateperone 28 mg once daily.[4] Inclusion and exclusion were essentially the same, with the exclusion for use of injectable antipsychotics within 1.5 treatment cycles (administration interval for each medication), rather than 1 treatment cycle.[4] Baseline demographics were primarily male (77.1%), African-American (66.4%), and with a mean age of 42.4 years [standard deviation (SD) 10.2 years].[4] The baseline mean PANSS was 89.8 (SD 10.5) and time since schizophrenia diagnosis of 17.0 years (SD 10.5 years).[4] The mean PANSS change from baseline using a mixed-effect model repeated measures was -15.6 for lumateperone 42 mg (LS mean difference from placebo -4.2, 95% CI -7.8 to -0.6; ES -0.3, p=0.02) and -13.7 for lumateperone 28 mg (LS mean difference from placebo -2.6, 95% CI -6.2 to 1.1; ES -0.18, p=0.16), compared to -12.4 for placebo.[4]

A third, unpublished, double-blind RCT (NCT02469155) compared lumateperone 42 mg, lumateperone 14 mg, and risperidone 4 mg (each dosed once daily) to placebo after 6 weeks of inpatient treatment (n=696).[5] The demographic, baseline, and inclusion/exclusion criteria for this trial were similar to the previous two.[5] There were 31 (12.2%) patients in the ITT group with major protocol violations, usually due to a positive substance abuse drug screen during the treatment period or concomitant use of psychotropic medication other than lorazepam, benztropine, or propranolol.[5] An FDA reviewer noted that this was not expected to greatly affect the efficacy endpoint analysis.[5] The primary endpoint of change in total PANSS score from baseline to end of treatment at 6 weeks resulted in no difference compared to placebo for lumateperone 14 mg (LSM -15.0 $\pm$ SEM 1.3; placebo subtracted difference 0.1, 95% CI -3.4 to 3.5) and lumateperone 42 mg (LSM -14.6 $\pm$ SEM 1.2; placebo subtracted difference 0.5, 95% CI -2.9 to 3.8), though risperidone 4 mg did differentiate from placebo (LSM -20.5 $\pm$ SEM 1.3; placebo subtracted difference -5.4, 95% CI -8.9 to -1.9).[5] Study discontinuation due to lack of efficacy were highest in the placebo (6.9%), lumateperone 14 mg (7.5%), and lumateperone 42 mg (6.3%) groups compared to risperidone 4 mg (4.6%).[5] Completion of the medication treatment period was as follows: lumateperone 14 mg (67.8%), lumateperone 42 mg (74.7%), risperidone 4 mg (62.6%) and placebo (78.7%). Overall study completion, after conversion to non-study APDs and outpatient follow-up 2 weeks after final study dose, resulted in additional attrition.[5] Notably, this study was the longest and the largest of the three studies, which increases concern that the primary endpoint was not achieved.

These studies suffered from risk of internal biases and applicability concerns (Table 4). These include risk of reporting bias related to funding of research, possible publication bias, and inconsistency in results between studies and between doses. The presence of an active control group (risperidone) was used in two studies, but without a priori analysis for between group comparisons, the comparative efficacy increases uncertainty in these results. The short duration of these studies and use in only the inpatient setting limit real world applicability. Additionally, the significant attrition with these inpatients studies leaves questions and concerns about outpatient medication adherence.

Clinical Safety:
Lumateperone carries many of the same warnings and precautions of other SGAs. Elderly patients with dementia-related psychosis are at increased risk of death, including fatal stroke, as well as overall incidence of stroke and transient ischemic attacks.[102] Other class-wide warnings include risk of neuroleptic malignant syndrome and tardive dyskinesia.[102] Second-generation antipsychotic use can result in metabolic changes such as hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain; these adverse reactions have been reported in patients using lumateperone.[102] Leukopenia, neutropenia, agranulocytosis, orthostatic hypotension, syncope, falls, seizures, body temperature dysregulation, and dysphagia are additional class-based precautions.[102] Lumateperone is contraindicated in those with history of hypersensitivity to the agent, and reactions may present as pruritis, rash, and urticaria.[102]

The Lieberman et al. Phase 2 trial did not have any serious adverse events associated with lumateperone tosylate over 4 weeks, though serious worsening of schizophrenia and psychosis did occur in one risperidone and one placebo participant.[3] Two patients discontinued lumateperone tosylate secondary to an adverse events (dry mouth and worsening schizophrenia), while there were 3 associated with risperidone use (elevated creatine phosphokinase and 2 cases of akathisia).[3] Rates of akathisia were similar to placebo for both doses of lumateperone, while risperidone had the highest rates of akathisia (placebo 2.3%; lumateperone tosylate 60 mg 1.2%; lumateperone tosylate 120 mg 2.4%; risperidone 4 mg 7.3%).[3] Mean weight change from baseline was increased in all active treatment groups [placebo 0.83 kg (95% CI 0.00-1.67); lumateperone tosylate 60 mg, 2.01 kg (95% CI 1.27-2.75 kg); lumateperone tosylate 120 mg, 1.93 kg (95% CI 1.13-2.73 kg); risperidone 4 mg, 3.01 kg (2.13-3.90 kg)].[5]

In the Correll et al. study, there were 2 patients with severe treatment emergent adverse event (TEAE) resulting in discontinuation, one in the lumateperone 42 mg group with orthostatic hypotension and one in the lumateperone 28 mg group with convulsions who had preexisting risk factors and a relevant medical history regarding seizures.[4] Additional discontinuations occurred in 2 patients in the lumateperone 42 mg group due to headache, and one in the placebo group due to presumed worsening of schizophrenia.[4] There was no association with suicidal ideation (lumateperone 42 mg 1.4%; lumateperone 28 mg 1.4%; placebo 1.4%) or suicidal behavior (0% all groups) as measured by the Columbia Suicide Severity Rating Scale.[4] Akathisia was seen in similar rates among the three study groups (lumateperone 42 mg 4%; lumateperone 28 mg 1.3%; placebo 2.7%).[4] Weight gain of greater than or equal to 7% with a shift from an overweight to obese BMI increased with dose (lumateperone 42 mg 8.4%; lumateperone 28 mg 4.3%; placebo 3.8%), though the median change in weight was similar among all groups (lumateperone 42 mg 0.9 kg; lumateperone 28 mg 0.6 kg; placebo 0.7 kg).[4]

One patient in the unpublished study withdrew after a serious adverse event of agitation secondary to worsening psychosis from the lumateperone 42 mg arm.[5] Somnolence, fatigue, and sedation were the most common TEAEs (lumateperone 42 mg 23.6%; lumateperone 14 mg 17.2%; risperidone 4 mg 26%; placebo 9.8%).[5] Common TEAEs from all 3 studies included creatine phosphokinase increases, dry mouth, fatigue, somnolence/sedation, dizziness, increased transaminases, nausea, vomiting, and decreased appetite.[5] Long-term safety data are lacking in light of study durations of only 4-6 weeks. As with other SGAs, long-term data related to metabolic risk factors and weight gain are vital.

Table 2: Pooled Adverse Events from 4- to 6-week duration Schizophrenia trials[102]

Adverse event	Lumateperone 42 mg (%) (n=406)	Placebo (%) (n=412)
Somnolence/Sedation	24	10
Nausea	9	5
Dry mouth	6	2
Dizziness	5	3
Increased creatine phosphokinase	4	1
Fatigue	3	1
Vomiting	3	2
Increased hepatic transaminases	2	1
Decreased appetite	2	1

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction of symptoms of psychosis
2) Improved quality of life or function
3) Reduction of positive or negative or depression symptoms
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in PANSS from baseline

Table 3 Pharmacology and Pharmacokinetic Properties.[102]

Parameter	
Mechanism of Action	Unknown, likely mediated via antagonism of central serotonin 5-HT_{2A} receptors and postsynaptic antagonism of central dopamine D_2 receptors.
Oral Bioavailability	4.4%, High-fat meal increases C_{max} by 33% and AUC by 9%
Distribution and Protein Binding	Volume of distribution 4.1 L/kg Protein binding 97.4% (when tested at 70-fold higher than therapeutic concentrations)
Elimination	Clearance of 27.9 L/hr; 58% urine, 29% feces, less than 1% unchanged in urine
Half-Life	18 hr
Metabolism	Extensive metabolism via multiple enzymes with more than 20 metabolites. Enzymes include: uridine 5'-diphospho-glucuronsultransferases 1A1, 1A4, 2B15; aldoketoreductase 1C1, 1B10, 1C4; cytochrome P450 3A4, 2C8, 1A2.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; hr = hour; L = liter; kg = kilogram

Table 4. Comparative Evidence Table: lumateperone

Ref./ Study Design	Drug Regimens*/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Lieberman JA, et al.[3] MC, DB, RCT phase II NCT 1499563	1. Placebo 2. Lumateperone tosylate 60 mg (equiv to 42 mg) 3. Lumateperone tosylate 120 mg (equiv to 84 mg)	Demographics: Male: 82.6% Age: mean 40.1y Black: 78.1% Baseline PANSS: 91.2 Key Inclusion Criteria: 1. Age 18-55 years	Rand: N=335 1. 85 2. 84 3. 83 4. 82 mITT: N=311 1. 80	Primary Endpoint: Change from baseline to day 28 on PANSS score vs placebo LSM (± SEM) 1. -7.4 ± 1.68 2. -13.4 ± 1.69 (p=0.017) 3. -8.3 ± 1.68 (p=0.708)	NA	Serious AE: 1. 1 2. 0 3. 0 4. 1 AE causing discontinuation: 1. 0 2 or 3.[†] 2	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Inclusion qualifications verified by both study investigators and independent psychiatrists or clinical psychologists as a doublecheck against subjectivity in scales used. Randomization via automated telephone or web-based system with allocation concealment using unique randomized number for a numbered kit

	4. Risperidone 4 mg Daily dose in the AM x 4 weeks inpatient therapy then transitioned and stabilized on standard APD for 5 days and discharged Safety visit 2 weeks post-final study dose	2. Diagnosis of schizophrenia by DSM-CTV 3. Acute exacerbation of psychosis (≥40 on Brief Psychiatric Rating Scale) 4.Episode starting within 4 wks of screening 5. Not treatment-resistant OR treatment-naïve <u>Key Exclusion Criteria</u>: 1. Presence of: dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma, schizoaffective d/o, bipolar d/o, acute mania, major depression w/ psychotic features, imminent danger to self or others, suicidal ideation/behavior, unstable living environment, use of depot antipsychotic within 1 treatment cycle, use of any antipsychotic in screening period, use of agents with 5-HT2A receptor interaction 2. Cardiovascular, renal, hepatic, endocrine, neurological dz or	2. 76 3. 80 4. 75 <u>Safety:</u> N=334 (received 1+ dose study drug <u>Inpatient Attrition</u>: 1. 19 (22%) 2. 17 (20%) 3. 14 (17%) 4. 15 (18%) <u>Completed study safety visit</u>: 1. 61 (72%) 2. 60 (71%) 3. 64 (76%) 4. 63 (77%)	4. -13.4 ± 1.72 (p=0.013) CI not reported <u>Secondary Endpoints</u>: Responder Analysis: PANSS decrease ≥ 30% 1. 18 (22.5%) 2. 31 (40.8%) 3. 20 (25%) 4. 30 (40%) 1 vs. 2: RD 18.3%, 95% CI 3.9 to 32.6; p=0.014 1 vs. 3: RD 2.5%, 95% CI -10.7 to 15.7; p=0.711 1 vs. 4: RD 17.5%, 95% CI 3.1 to 31.9; p=0.019 Subgroup analysis of patients through day 28 group with negative symptoms at baseline PANSS Negative subscale subgroup Mean (± SEM) from baseline (p vs placebo) 1. -1.3 ± 0.92 2. -3.0 ± 0.88 (p=0.206) 3. -1.1 ± 0.93 (p=0.865) 4. -1.2 ± 0.80 (p=0.893) Subgroup analysis of per protocol patients through day 28 group depression at baseline Total PANSS depression subgroup Mean (± SEM) from baseline (p vs placebo) 1. -12.4 ± 3.89 2. -31.7 ± 7.31 (p=0.018) 3. -14.2 ± 3.51 (p=0.736) 4. -20.6 ± 3.89 (p=0.152)	18.3%/5 NA 17.5%/6 NA	4. 3 Weight gain (kg) Median, Mean (SD) 1. 0.8, 0.8 (2.3) 2. 1.0, 2.0 (3.10) 3. 1.1, 1.9 (3.35) 4. 2.5, 3.0 (3.69) Sedation 1. 11 (12.9%) 2. 14 (16.7%) 3. 27 (32.5%) 4. 17 (20.7%)	NA NA	containing visually matched capsules. Groups were well matched. <u>Performance Bias</u>: (low) All are taking visually matched capsules to maintain blinding. <u>Detection Bias</u>: (low) Remote raters with training for interrater reliability and blinding to study design, treatment, and time point of assessment. Validated PANSS and CDSS used for assessment. <u>Attrition Bias</u>: (high) High overall attrition rate (19% at 28 days while inpatient and 26% by final safety visit). Last observation carried forward used for missing data. Approximately 2-fold higher attrition in placebo patients from "lack of efficacy" than other groups <u>Reporting Bias</u>: (high) Secondary endpoints difficult ascertain as a priori vs. post hoc between published study, FDA review document, and clinicaltrials.gov listing. <u>Other Bias:</u> (high) Funding provided by drug company and several authors had financial conflicts of interest. **Applicability**: <u>Patient</u>: Racial distribution not representative of normal disease distribution, though it more closely aligns to Oregon Medicaid population. Exclusion of treatment-naïve patients, treatment-resistant patients, and patients with other mental health conditions as well as exclusive inpatient use limits applicability. <u>Intervention</u>: Salt formulation used: 60 mg salt = 42 mg, 120 mg salt = 84 mg, with lack of dose response as 120 mg salt did not meet primary endpoint. <u>Comparator</u>: Placebo appropriate to establish efficacy, direct comparisons with risperidone group is more informative to clinical practice. <u>Outcomes</u>: Validated scales used to assess schizophrenia symptoms, longer duration of response needed to assess long term

		significant lab abnormalities 3. SA/dependence 4. Unable to be safely discontinued from current antipsychotic/psychotropic regimen		CDSS depression subgroup Mean (± SEM) from baseline (p vs placebo) 1. -5.4 ± 1.00 2. -7.7 ± 0.42 (p=0.044) 3. -5.6 ± 0.74 (p=0.839) 4. -7.2 ± 1.31 (p=0.271)				reduction in symptoms and safety. Quality of life data needed. Setting: 8 sites in US. Limited applicability to the outpatient setting.
2. Correll et al.[4] MC, DB, RCT, phase 3 NCT 2282761	1. Lumateperone 42 mg 2. Lumateperone 28 mg 3. Placebo Daily dose in the AM x 4 weeks inpatient therapy Then transitioned and stabilized on standard APD for 5 days and discharged Safety visit 2 weeks post-final study dose	Demographics: Male: 77.1% Age: mean 42.4y (SD ± 10.2) Black: 66.4% Baseline PANSS: 89.8 (SD ± 10.3) Key Inclusion Criteria: 1. 18-60 years 2. Diagnosis of schizophrenia by DSM-CTV 3. Acute exacerbation of psychosis (≥40 on Brief Psychiatric Rating Scale with ≥4 (range 1-7) on at least 2 positive symptoms) 4. Episode starting within 4 wks of screening 5. Mod-severe dz severity (CGI-S score ≥4) 6. Moderate-extreme schizophrenia (PANSS score ≥70) 7. Not treatment-resistant OR treatment-naïve Key Exclusion Criteria:	N=449 Rand: 1. 150 2. 150 3. 150 mITT: 1. 148 2. 146 3. 141 Safety: 1. 150 2. 150 3. 149 Attrition: 1. 14.7% 2. 20.0% 3. 26.0%	Primary Endpoint (MMRM): Change from baseline to day 28 on PANSS score vs placebo LSM (± SEM) 1. -14.5 ± 1.3 2. -12.9 ± 1.3 3. -10.3 ± 1.3 1 vs. 3: -4.2; 95% CI -7.8 to -0.6 (p=0.02) 2 vs. 3: -2.6; 95% CI -6.2 to 1.1 (p=0.16) Secondary Endpoints: CGI-S score: LSM (± SEM) 1. -0.8 ± 0.07 2. -0.8 ± 0.08 3. -0.5 ± 0.08 1 vs. 3: -0.3; 95% CI -0.5 to -0.1 (p=0.003) 2 vs. 3: -0.2; 95% CI -0.5 to 0.0) (p=0.003)	NA NA	Serious AE 1. 0 2. 1 3. 1 AE causing discontinuation: 1. 2 2. 2 3. 1 Death 1. 0 2. 0 3. 1 (13 days after discontinuing study) Weight gain (kg) Mean (range) 1. 0.9 (-36 to 11) 2. 0.6 (-12 to 13) 3. 0.7 (-12 to 16) Sedation/ Somnolence 1. 45 (30.0%) 2. 31 (20.6%) 3. 14 (9.4%)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Central randomization via automated telephone or web-based system. Unique randomization number assigned to each patient with dispensing of identical capsules from patient kit by pharmacist or staff member. Performance Bias: (low) Investigators, study staff at clinical site, patients, primary study team, and sponsor blinded to study treatment. Visually matched capsule dispensed by pharmacy or designated staff member. Detection Bias: (low) Primary and some secondary efficacy endpoints measured via videoconference by trained central raters, blinded to treatment and study visit. Additional secondary and safety endpoints assessed by trained raters at individual study sites. Validated PANSS and CDSS used for assessment. Attrition Bias: (high) Significant attrition overall (18.7% by end of inpatient treatment and 20.2% through final safety visit). Higher rate from withdrawal of consent and lack of efficacy, indicating possible unblinding in placebo group (placebo 22.1%, lumateperone 42 mg 10.7%, lumateperone 28 mg 12.7%). Missing data not imputed based on assumption that data is missing at random, which may be inappropriate given differential attrition between placebo and active groups. Reporting Bias: (high) Funding provided by drug company who contributed to all aspects of study from design to publication decision.

		1. Presence of: dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, brain trauma, schizoaffective d/o, bipolar d/o, acute mania, major depression w/ psychotic features, imminent danger to self or others, suicidal ideation/behavior, unstable living environment, use of depot antipsychotic within 1.5 treatment cycle, use of any antipsychotic in screening period, use of agents with 5-HT2A receptor interaction 2. Cardiovascular, renal, hepatic, endocrine, neurological dz or significant lab abnormalities 3. SA/dependence 4. Unable to be safely discontinued from current antipsychotic/psychotropic regimen						Several authors had financial conflicts of interest. **Applicability**: Patient: Racial distribution not representative of normal disease distribution, though it more closely aligns to Oregon Medicaid population. Exclusion of treatment-naïve patients, treatment-resistant patients, and patients with other mental health conditions as well as exclusive inpatient use limits applicability. Intervention: Highest dose in this study (42 mg) is only FDA approved dose. Comparator: Placebo appropriate to establish efficacy, active comparator would be more informative to clinical practice. Outcomes: Validated scales used to assess schizophrenia symptoms, longer duration of response needed to assess long term reduction in symptoms and safety. Quality of life data needed. Setting: 12 sites in US. Limited applicability to the outpatient setting.

Abbreviations: Adverse event = AE; ARR = absolute risk reduction; CDSS = Calgary depression scale for schizophrenia; CGI-S = Clinical Global Impression-Severity of Illness; CI = confidence interval; CPK = creatine phosphokinase; DB = double blind; d/o = disorder; DSM-CTV = Diagnostic and Statistical Manual of Mental Disorders-clinical trials version; dz = disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human Immunodeficiency virus; hx = history; ITT = intention to treat; LAE = liver associated enzymes; LSM = least squares of the mean; kg = kilograms; MC = multicenter; mITT = modified intention to treat; MMRM = mixed-effect model repeated measures; N = number of subjects; NA = not applicable; NMS = neuroleptic malignant syndrome; NNH = number needed to harm; NNT = number needed to treat; PANSS = positive and negative syndrome scale ; PP = per protocol; PSQI = Pittsburg Sleep Quality Index; Rand = Randomized ; RD = rate difference; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; SEM = standard error of the mean; tx = treatment; US = Unites States, y = years

* Lumateperone tosylate 40 mg = lumateperone 28 mg; Lumateperone tosylate 60 mg = lumateperone 42 mg; Lumateperone tosylate 120 mg = lumateperone 84 mg

† Treatment assignment unclear

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Appendix 1: Current Preferred Drug List

1st Generation oral antipsychotics

Generic	Brand	Route	Formulation	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL	TABLET	Y
fluphenazine HCl	PROLIXIN	ORAL	TABLET	Y
haloperidol	HALOPERIDOL	ORAL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL	ORAL CONC	Y
loxapine succinate	LOXAPINE	ORAL	CAPSULE	Y
perphenazine	PERPHENAZINE	ORAL	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL	TABLET	Y
thiothixene	THIOTHIXENE	ORAL	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL	ORAL CONC	Y
trifluoperazine HCl	STELAZINE	ORAL	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	ORAL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL	TABLET	V
chlorpromazine HCl	THORAZINE	ORAL	TABLET	V
loxapine	ADASUVE	INHALATION	AER POW BA	V
pimozide	PIMOZIDE	ORAL	TABLET	V

2nd Generation oral antipsychotics

Generic	Brand	Route	Formulation	PDL
asenapine maleate	SAPHRIS	SUBLINGUAL	TAB SUBL	Y
cariprazine HCl	VRAYLAR	ORAL	CAP DS PK	Y
cariprazine HCl	VRAYLAR	ORAL	CAPSULE	Y
clozapine	CLOZAPINE	ORAL	TABLET	Y
clozapine	CLOZARIL	ORAL	TABLET	Y
lurasidone HCl	LATUDA	ORAL	TABLET	Y
olanzapine	OLANZAPINE	ORAL	TABLET	Y
olanzapine	ZYPREXA	ORAL	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	ORAL	TABLET	Y
quetiapine fumarate	SEROQUEL	ORAL	TABLET	Y

risperidone	RISPERDAL	ORAL	SOLUTION	Y
risperidone	RISPERIDONE	ORAL	SOLUTION	Y
risperidone	RISPERDAL	ORAL	TABLET	Y
risperidone	RISPERIDONE	ORAL	TABLET	Y
aripiprazole	ARIPIPRAZOLE	ORAL	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	ORAL	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	ORAL	TAB SENSPT	V
aripiprazole	ABILIFY	ORAL	TABLET	V
aripiprazole	ARIPIPRAZOLE	ORAL	TABLET	V
asenapine	SECUADO	TRANSDERM	PATCH TD24	V
brexpiprazole	REXULTI	ORAL	TABLET	V
clozapine	VERSACLOZ	ORAL	ORAL SUSP	V
clozapine	CLOZAPINE ODT	ORAL	TAB RAPDIS	V
clozapine	FAZACLO	ORAL	TAB RAPDIS	V
olanzapine	OLANZAPINE ODT	ORAL	TAB RAPDIS	V
olanzapine	ZYPREXA ZYDIS	ORAL	TAB RAPDIS	V
paliperidone	INVEGA	ORAL	TAB ER 24	V
paliperidone	PALIPERIDONE ER	ORAL	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	ORAL	CAPSULE	V
pimavanserin tartrate	NUPLAZID	ORAL	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	ORAL	TAB RAPDIS	V
ziprasidone HCl	GEODON	ORAL	CAPSULE	V
ziprasidone HCl	ZIPRASIDONE HCL	ORAL	CAPSULE	V

Parenteral antipsychotics

Generic	Brand	Route	Form	PDL
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER VIAL	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER VIAL	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y

aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil	ARISTADA	INTRAMUSC	SUSER SYR	Y
aripiprazole lauroxil,submicr.	ARISTADA INITIO	INTRAMUSC	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	INJECTION	AMPUL	Y
chlorpromazine HCl	THORAZINE	INJECTION	AMPUL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	INJECTION	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	INJECTION	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 50	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	INTRAMUSC	AMPUL	Y
haloperidol lactate	HALDOL	INJECTION	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INJECTION	VIAL	Y
haloperidol lactate	HALOPERIDOL LACTATE	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	INTRAMUSC	SYRINGE	Y
risperidone	PERSERIS	SUB-Q	SUSER SYKT	Y
risperidone	PERSERIS	SUB-Q	SUSER SYKT	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
risperidone microspheres	RISPERDAL CONSTA	INTRAMUSC	VIAL	Y
trifluoperazine HCl	STELAZINE	INTRAMUSC	VIAL	Y
olanzapine	OLANZAPINE	INTRAMUSC	VIAL	V

olanzapine	ZYPREXA	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	INTRAMUSC	VIAL	V
ziprasidone mesylate	GEODON	INTRAMUSC	VIAL	V
ziprasidone mesylate	ZIPRASIDONE MESYLATE	INTRAMUSC	VIAL	V

Appendix 2: Abstracts of Comparative Clinical Trials
None

Appendix 3: Medline Search Strategy

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

Search performed March 13, 2020

1	Chlorpromazine/ae, tu, th [Adverse Effects, Therapeutic Use, Therapy]	5346
2	Fluphenazine/ae, tu [Adverse Effects, Therapeutic Use]	1218
3	Haloperidol/ae, tu [Adverse Effects, Therapeutic Use]	5212
4	Loxapine/ae, tu [Adverse Effects, Therapeutic Use]	189
5	Perphenazine/ae, tu [Adverse Effects, Therapeutic Use]	591
6	Thioridazine/ae, tu [Adverse Effects, Therapeutic Use]	1132
7	Thiothixene/ae, tu [Adverse Effects, Therapeutic Use]	259
8	Trifluoperazine/ae, tu [Adverse Effects, Therapeutic Use]	612
9	Pimozide/ae, tu [Adverse Effects, Therapeutic Use]	496
10	asenapine.mp.	407
11	cariprazine.mp.	197
12	Clozapine/ae, tu [Adverse Effects, Therapeutic Use]	5217
13	Lurasidone Hydrochloride/ae, tu [Adverse Effects, Therapeutic Use]	90
14	Olanzapine/ae, tu [Adverse Effects, Therapeutic Use]	152
15	Quetiapine Fumarate/ae, tu [Adverse Effects, Therapeutic Use]	359
16	Risperidone/ae, tu [Adverse Effects, Therapeutic Use]	4664
17	Aripiprazole/ae, tu [Adverse Effects, Therapeutic Use]	442
18	brexpiprazole.mp.	189
19	Paliperidone Palmitate/ae, tu [Adverse Effects, Therapeutic Use]	202
20	pimavanserin.mp.	170
21	ziprasidone.mp.	1997
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	25047
23	limit 22 to yr="2019 -Current"	498
24	limit 23 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv 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")	85
25	limit 24 to humans	84
26	limit 25 to English language	82
27	Lumateperone.mp.	13
28	limit 27 to (English language and humans)	6
29	26 or 28	88

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

CAPLYTA (lumateperone) capsules, for oral use
Initial U.S. Approval: 2019

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis. (5.1)

----------INDICATIONS AND USAGE----------
CAPLYTA is an atypical antipsychotic indicated for the treatment of schizophrenia in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of CAPLYTA is 42 mg once daily. (2.1)
- Administer CAPLYTA with food. (2.1)
- Dose titration is not required. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 42 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to lumateperone or any components of CAPLYTA. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke and transient ischemic attack). (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Tardive Dyskinesia:* Discontinue treatment if clinically appropriate. (5.4)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.5)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors. (5.6)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- *Seizures:* Use cautiously in patients with a history of seizure or with conditions that lower seizure threshold. (5.9)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.10)

----------ADVERSE REACTIONS----------
Most common adverse reactions in clinical trials (incidence ≥ 5% and greater than twice placebo) were somnolence/sedation and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intra-Cellular Therapies, Inc. at 1-888-611-4824 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CYP3A4 inducers: Avoid concomitant use. (2.2, 7.1)
- Moderate or strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Lactation: Breastfeeding not recommended. (8.2)
- Moderate or severe hepatic impairment: Avoid use. (2.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

Appendix 5: Key Inclusion Criteria

Population	**Adults with schizophrenia**
Intervention	Antipsychotic medications
Comparator	Placebo, active control
Outcomes	Clinical effectiveness, safety
Timing	n/a
Setting	Inpatient or outpatient

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 (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

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

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

Table 2. Pediatric FDA-approved indications

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (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 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 for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *8/2020 (SF); 3/19 (DM); 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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 treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
6. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *8/2020 (SF); 3/19 (DM); 9/18; 3/18; 01/17*
Implementation: *4/1/17*

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

Date of Review: August 2020

Date of Last Review: March 2017
Dates of Literature Search: 01/01/2017 – 01/09/2020
Brand Name (Manufacturer): Beovu® (Novartis)
Dossier Received: yes

Generic Name: brolucizumab-dbll

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

Purpose for Class Update:
To evaluate new comparative evidence for vascular endothelial growth factors (VEGF) inhibitors for ocular conditions and place in therapy of brolucizumab, a new molecular entity approved by the Food and Drug Administration (FDA) in 2019 for neovascular age-related macular degeneration (AMD).

Research Questions:
1. What is the evidence for comparative efficacy of VEGF inhibitors for ocular conditions?
2. What is the evidence for comparative safety of VEGF inhibitors for ocular conditions?
3. Are there any subpopulations (based on patient or disease characteristics) for which a specific agent may be more effective or associated with less harm?

Conclusions:
- Current evidence indicates that there is no clinically meaningful difference in best corrected visual acuity (BCVA) between ranibizumab, bevacizumab, or aflibercept in patients treated for diabetic macular edema (DME), neovascular AMD, or macular edema associated with retinal vein occlusion (RVO) based on moderate to high quality evidence.[1-4]
- Evidence on the risk of serious adverse events between VEGF inhibitors is mixed. However, new literature did not identify any new safety signals for VEGF inhibitors and indicates the risk for serious thromboembolic or ocular adverse effects (including endophthalmitis, eye pain, macular hole, macular edema, retinal hemorrhage or reduced visual acuity) is likely comparable between agents (low to moderate quality evidence).[1-5]
- There is moderate quality evidence that brolucizumab is non-inferior to aflibercept at 48 weeks based on BCVA in patients with neovascular AMD.[6]
- There is insufficient evidence on long-term safety of brolucizumab beyond 2 years. Labeling for brolucizumab is consistent with other VEGF inhibitors and includes warnings for thromboembolic and serious ocular adverse events.[7]

Recommendations:
- No PDL changes recommended based on clinical evidence. Evaluate costs in executive session.

Author: Sarah Servid, PharmD

Summary of Prior Reviews and Current Policy

- There is high to moderate quality evidence of no difference in best corrected visual acuity between ranibizumab and bevacizumab or ranibizumab and aflibercept for neovascular AMD.
- There is moderate quality evidence of no clinical meaningful difference in efficacy (defined as a change of >15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) between anti-VEGF agents in patients treated for diabetic macular edema.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.
- There is no difference in serious ocular events between ranibizumab, bevacizumab or aflibercept (low quality evidence). Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed, though higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between agents. Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).
- Bevacizumab is the current preferred product. All other VEGF inhibitors are non-preferred.

Background:

Vascular endothelial growth factor (VEGF) inhibitors are indicated for a wide variety of ocular conditions. FDA-approved indications differ between agents, but commonly include macular edema associated with diabetic retinopathy or retinal vein occlusion, neovascular age-related macular degeneration (AMD), and myopic choroidal neovascularization. In these diseases, vascular damage can trigger inflammatory responses, expression of VEGF, and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[8] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[8] Intraocular injections of VEGF inhibitors work to prevent vascular endothelial growth factor expression in late stage disease, thereby preventing further choroidal neovascularization and preserving vision in these populations.[8]

These ocular conditions are often categorized according to the type of retinal abnormalities present including presence or absence of neovascularization or macular edema. With presence of neovascularization or macular edema, VEGF inhibitors are typically indicated as a first-line treatment option. Guidelines from the American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first-line therapy for macular edema associated with branched or central retinal vein occlusion, neovascular AMD, and clinically significant diabetic macular edema associated with vision loss.[8] No recommendations are made for any specific agent. Similar guidelines are available from National Institute for Health and Care Excellence (NICE) which recommend VEGF inhibitors as first-line therapy for neovascular AMD and recommend use for myopic choroidal neovascularization and macular edema associated with retinal vein occlusion or diabetes.[1,9-11] Alternative treatment options vary by condition and disease characteristics, but can include intraocular steroids, laser photocoagulation, and pan-retinal photocoagulation. In patients with other associated complications of diabetic retinopathy, these non-pharmacological options may be preferred or used in combination with VEGF inhibitors.[12]

VEGF inhibitors used most commonly in practice in the United States (US) include bevacizumab, ranibizumab and aflibercept. See **Table 1** for a list of FDA-approved ocular indications. While bevacizumab is not FDA-approved for any ophthalmic indications, there is a substantial body of evidence supporting off-label use.

Table 1. FDA-approved ophthalmic indications for VEGF inhibitors

Generic Drug Name (Brand)	Neovascular AMD	Macular Edema Following RVO	Diabetic Retinopathy	Diabetic Macular Edema	Myopic Choroidal Neovascularization
Aflibercept (Eylea®)	**X**	**X**	**X**	**X**	
Bevacizumab (Avastin®)					
Brolucizumab (Beovu®)	**X**				
Pegaptanib sodium (Macugen®)	**X**				
Ranibizumab (Lucentis®)	**X**	**X**	**X**	**X**	**X**

Abbreviations:AMD = age related macular degeneration; RVO = retinal vein occlusion

In clinical trials, visual acuity changes are often evaluated using the ETDRS chart. The minimal clinically important difference referenced in the literature can vary, but a change of 5 letters (corresponding to 1 line on the chart) is typically considered to be the minimum clinically detectable change.[1] For many conditions, moderate visual gains or losses are defined as changes of at least 10 to 15 letters (corresponding to approximately 2-3 lines).[1]

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

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

Systematic Reviews:

CADTH evaluated the safety of VEGF inhibitors in 2 systematic reviews. The first review assessed risk factors for development of acute, sustained intraocular pressure increases following VEGF administration.[13] Overall there was insufficient evidence assessing risk factors for sustained intraocular pressure requiring medical or surgical intervention and insufficient comparative evidence between VEGF agents.[13] Evidence was limited by high heterogeneity between identified studies, lack of consistently reported outcomes, and variable follow-up periods.[13] A second CADTH report evaluated ocular and cardio-thromboembolic adverse events.[5] The report included a descriptive analysis of 5 systematic reviews (including over 30 RCTs), and multiple large, retrospective, observational studies which compared incidence of adverse events with bevacizumab, ranibizumab, and aflibercept.[5] One of the included systematic reviews, published in 2012, noted a slightly increased risk of serious ocular adverse events associated with bevacizumab compared to ranibizumab or aflibercept.[5] However, 3 subsequent systematic reviews have failed to identify an increased risk with bevacizumab upon incorporation of data from new RCTs.[5] Similarly, a single center retrospective cohort study identified a higher risk of endophthalmitis with bevacizumab compared to ranibizumab.[5] However, this study had high risk of selection bias from imbalances in baseline characteristics and was limited by inclusion of only one study site. Other observational studies with lower risk of bias have failed to identify differences in incidence between agents. Overall, incidence of endophthalmitis was low, ranging from 0% to 0.11% for all studies.[5] Of the observational studies assessing risk for thromboembolic events, none identified a difference in risk between VEGF inhibitors.[5] Data are limited by lack of large, well-designed

RCTs powered to detect differences in adverse events. However, this data does not identify any new safety signals for VEGF inhibitors and indicates risk is likely comparable between agents.

A 2019 systematic review evaluated the comparative efficacy and safety of VEGF inhibitors for treatment of neovascular AMD, DME and RVO.[2] The review included 24 publications of 17 RCTs. Most studies (n=11) evaluated patients with neovascular AMD.[2] In patients with AMD, there was no difference in mean BCVA or proportion of patients gaining 15 or more letters at 12 months or 18-24 months upon comparison of bevacizumab and ranibizumab.[2] Two trials compared aflibercept and ranibizumab with low quality evidence of no clinical difference between agents based on mean change in BCVA and proportion of patients gaining 15 or more letters.[2] Data for this comparison was limited by high heterogeneity between trials. There was no direct comparative evidence for aflibercept and bevacizumab in neovascular AMD.[2] Three trials compared bevacizumab to ranibizumab in patients with DME and found no difference in mean BCVA (MD 2.0 letters; 95% CI −0.4 to 4.4) or proportion of patients gaining 15 or more letters at 24 months.[2] One trial comparing bevacizumab to aflibercept in DME found statistical improvements in mean BCVA with aflibercept at 12 months (MD 3.5 letters; 95% CI 1.4 to 5.7) and 24 months (MD 2.7 letters; 95% CI 0.3 to 4.2) which did not meet the threshold for clinically important differences.[2] The proportion of patients with a gain of 15 or more letters was improved with aflibercept compared to bevacizumab at 12 months, but was not statistically significant at 24 months.[2] Subgroup analyses indicate that benefit of aflibercept may be improved particularly in patients with worse visual acuity at baseline (<69 letters) who appeared to have a statistical and slight clinical benefit with aflibercept versus bevacizumab at 12 months (MD 6.5 letters; 95% CI 2.9 to 10.1).[2] The difference observed at 24 months was smaller and did not meet the minimum difference for a clinically meaningful change (MD 4.7 letters; 95% CI 0.5 to 8.8; MCID of 5 letters).[2] Upon comparison of aflibercept to ranibizumab in one trial, there were small statistical differences in BCVA between the drugs at 12 months (MD 2.1 letters; 95% CI 0.1 to 4.2) which failed to meet the threshold for clinically important differences and were not sustained at 24 months.[2] Similar trends were noted for the subgroup with worse visual acuity at baseline with a small statistical benefit at 12 months (MD 4.7 letters; 95% CI 1.4 to 8.0) and no difference observed at 24 months (MD 2.3 letters; 95% CI −1.1 to 5.6).[2] One RCT compared aflibercept to bevacizumab in RVO with no differences based on mean BCVA and proportion of patients gaining 15 or more letters.[2] There was insufficient evidence from 2 RCTs comparing ranibizumab to bevacizumab. Evidence was limited by small sample size and imprecision. For the majority of trials included in this review, there was no difference in harms reported including serious ocular or systemic adverse events based on low to moderate evidence.[2] However, studies were not powered to detect differences in adverse events. For patients with neovascular AMD, only one in 5 trials identified a difference in systemic events with a higher rate with ranibizumab compared to bevacizumab at 12 months that was not observed at 24 months.[2] In this trial, evidence was limited by differences in baseline characteristics between groups. Bevacizumab was associated with more gastrointestinal events in 2 of 6 trials compared to ranibizumab.[2] In patients with DME, there was low quality evidence of no difference in serious ocular or systemic adverse events between agents. Upon analysis of individual adverse events, there was evidence from one trial that arterial thrombotic events may be higher with ranibizumab versus aflibercept (11.9% vs. 5.4%; p=0.047), but neither therapy was statistically different compared to bevacizumab (7.8%).[2] There was insufficient evidence on harms for patients with RVO.

Another high quality systematic review evaluating comparative effectiveness of VEGF inhibitors in patients with DME, neovascular AMD, RVO or myopic CNV reached similar conclusions.[3] The primary outcomes examined included vision gain of 15 or more letters, vision loss of 15 or more letters, mean change in BCVA, and progression to legal blindness (20/200).[3] Overall, they found no statistical differences in efficacy outcomes or serious harms between treatments for patients with neovascular AMD, DME, RVO or myopic CNV.[3] In a subgroup of patients with DME and with worse visual acuity at baseline (BCVA <69 letters), aflibercept had improved vision gain of 15 or more letters at 12 months (67%) compared to ranibizumab (50%) or bevacizumab (41%).[3] However, results were no longer statistically significant at 24 months (52%, 55%, and 58% for bevacizumab, ranibizumab, and aflibercept, respectively).[3]

A Cochrane systematic review of RCTs evaluated efficacy of pegaptanib, ranibizumab or bevacizumab for treatment of patients with neovascular AMD.[4] Outcomes pertaining to direct comparative evidence will be the focus of this discussion. There was no evidence comparing pegaptanib to other treatments. Ten trials were identified comparing bevacizumab to ranibizumab. The majority of trials had low risk of bias and reported no difference in mean BCVA (MD -0.5 letters 95% CI -1.5 to 0.4; n=3190 patients). Similarly, there was no difference in prevention of blindness in the study eye defined as BCVA > 20/200, gain of 15 or more letters, or loss of 15 or more letters at 1 or 2 years of treatment based on high quality evidence.[4] Only one trial evaluated quality of life or functional visual outcomes and had no difference observed between treatments (moderate quality evidence).[4] Patients treated with bevacizumab had less reduction in central retinal thickness at 12 months, though differences were small, within the range of measurement error, and not considered clinically significant (MD -11.6 µm, 95% CI -21.6 to -1.7; n=2693 patients; high quality evidence).[4] Similar results were seen after 2 years of treatment. There were no differences observed in serious systemic or ocular adverse events between treatments at 12 months, though studies were not powered to detect differences between groups.[4] Rate of serious adverse events at 2 years was slightly more common with bevacizumab compared to ranibizumab (36% vs. 30%; RR 1.20, 95% CI 1.05 to 1.37).[4] Upon analysis of individual adverse events at 2 years, gastrointestinal disorders were slightly more common with bevacizumab compared to ranibizumab (RR 2.74, 95% CI 1.49 to 5.02), and there was a trend toward more cardiac disorders with bevacizumab, though differences did not achieve statistical significance (RR 1.25, 95% CI 0.92 to 1.71).[4] Less than 2% of patients experienced a serious cardiovascular event after 2 years of therapy and serious ocular events occurred in less than 1% of patients receiving VEGF inhibitors.[4]

A 2018 systematic review from NICE was used to inform guidelines for the management of age-related macular degeneration.[1] Pharmacologic therapies evaluated as part of this guidance included aflibercept, ranibizumab, and bevacizumab. There was high quality evidence from 8 RCTs (n=3101) of no difference in visual acuity between bevacizumab and ranibizumab after 1 year of treatment based on outcomes of mean change in BCVA (MD -0.48 ETDRS letters, 95% CI -1.47 to 0.51), gain of 15 or more letters (RR 0.96; 95% CI 0.85 to 1.08) and loss of less than 15 letters (RR 1.00; 95% CI 0.98 to 1.02).[1] Similarly, there was high quality evidence from 2 RCTs (n=2412) of no difference in visual acuity between aflibercept and ranibizumab after 1 year of treatment based on mean change (MD -0.15 ETDRS letters; 95% CI -1.47 to 1.17) and gain of 15 or more ETDRS letters (RR 0.97; 95% CI 0.85 to 1.11).[1] No difference was observed in vision-related or health-related quality-of-life between treatments (moderate to high quality evidence).[1] There was moderate quality evidence that patients treated with bevacizumab received more injections over the course of a year compared to patients treated with ranibizumab (MD 0.60; 95% CI 0.33 to 0.87). No difference in serious systemic adverse events (including myocardial infarction, stroke, venous thrombotic events) or serious ocular adverse events (e.g., severe uveitis, retinal pigment epithelial tear, cataract, endophthalmitis, retinal tear) was observed between bevacizumab and ranibizumab (low quality evidence) or between ranibizumab and aflibercept (moderate quality evidence) with one year of treatment.[1] Compared to ranibizumab, patients treated with bevacizumab were more likely to have gastrointestinal disorders (RR 1.85; 95% CI 1.01 to 3.40; 5 RCTs, n=3038 people).[1]

In a subgroup analysis comparing patients varying levels of visual acuity, patients with BCVA better than 20/40 at baseline (approximately 70 ETDRS letters) had better visual acuity with VEGF inhibitor treatment at 1 year compared to patients with BCVA of 20/40 to 20/320 (MD 16.52 letters; 95% CI 13.41 to 19.64; low quality evidence).[1] However, compared to patients presenting with worse visual acuity at baseline, this subgroup also was more likely to have more visual acuity loss at 1 year (MD -6.34; 95%CI -7.33 to -5.36) and 5 years (MD -11.75; 95%CI -18.98 to -4.92) and less likely to have a gain in 15 or more ETDRS letters after 1 year of VEGF inhibitor treatment (RR 0.16; 95% CI 0.12 to 0.22).[1] Patients with baseline visual acuity worse than 6/96 were more likely to continue to have worse visual acuity after 1 year of treatment compared to patients with BCVA between 20/40 and 20/320 (MD -17.23 letters; 95% CI -22.36 to -12.10).[1] However, they were also more likely to gain more letters after 1 year of VEGF inhibitor treatment compared to those with better baseline BCVA (MD 13.99 letters; 95% CI 10.39 to 17.59).[1]

There was high quality evidence that BCVA was not improved at 6-12 months with use of combination VEGF inhibitor and photodynamic therapy compared to monotherapy with a VEGF inhibitor (MD −0.54; 95% CI −1.29 to 0.21).[1] More patients given monotherapy gained 15 or more letters compared to combination therapy at 6 to 12 months (RR 0.76; 95% CI 0.63 to 0.92; moderate quality evidence).[1] Patients given combination therapy received fewer VEGF inhibitor doses over 6 to 12 months (MD −0.94; 95% CI: −1.76 to −0.12).[1] No difference was seen in ocular or systemic adverse events. Similarly, there was no difference observed in BCVA, adverse events and number of injections for patients given combination VEGF inhibitors and steroids compared to VEGF inhibitor monotherapy. Evidence supporting switching therapies was all of low or very low quality and identified no clinical difference in BCVA upon switching between VEGF inhibitors.[1]

An analysis of different treatment regimens (e.g., PRN vs. routine injections vs. treat-and-extend) was also conducted. A treat-and-extend strategy involves progressive extension of routine treatment intervals for up to 12 weeks based on clinical findings, whereas a PRN regimen involves injections only if there is active progressive disease. Upon comparison of a PRN strategy to routine injections, there was moderate quality evidence that use of PRN regimens have worse visual acuity compared to routine injections (MD -1.45; 95% CI -2.45 to -0.45).[1] However, differences were not considered clinically significant (> 5 ETDRS letters), and there was no difference in the proportion of patients who had substantial visual changes (gain or loss of 15+ EDTRS letters) based on low and moderate quality evidence, respectively.[1] Patients treated with PRN regimens were less likely to have serious ocular adverse events compared with routine injections based on low quality evidence (RR 0.31; 95% CI 0.13 to 0.78).[1] No difference was observed in serious systemic adverse events (very low quality evidence). On average, patients using a PRN regimen had on average 4.22 fewer injections over the year (95% CI −4.72 to −3.73).[1] There is moderate quality evidence that visual acuity or adverse events did not differ between treat-and-extend compared to monthly regimens. Patients on the treat-and-extend regimens received on average 2.4 fewer injections per year (95% CI -2.8 to -2.0).[1] Compared to patients with longer time between injections, patients with routine injections at least every 6 weeks had better visual improvement (gain of 15+ ETDRS letters RR 1.28; 95%CI 1.08 to 1.52), but no clinical difference in visual loss (loss of fewer than 15 EDTRS letters) or average visual acuity.[1]

After review, 25 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
NICE guidelines for diagnosis and management of AMD were published in 2018.[1] This guideline included evidence for aflibercept, ranibizumab, and bevacizumab. No specific recommendations are made for any of these agents as no clinically significant differences in effectiveness or safety were observed for VEGF inhibitors. While switches in therapy can be considered for practical reasons, there is not expected to be any clinical benefit from switching therapy.[1] While there are no direct comparisons of these agents to pegaptanib, current NICE guidance does not recommend pegaptanib for neovascular AMD based on a previous review evaluating indirect comparisons to ranibizumab which indicate it may have less efficacy and higher cost.

The following recommendations guide use of VEGF inhibitors for the management of neovascular AMD:[1]

- VEGF inhibitors are recommended for patients with BCVA between 6/12 and 6/96 with evidence of recent disease progression (e.g., visual acuity changes or blood vessel growth). Evidence demonstrates that treatment is effective for patients with visual acuity better than 6/12 and may be cost effective depending on the agent used. For patients with visual acuity of less than 6/96, consider administration only if a benefit to the overall visual function is expected.
- Consider observation only in patients with stable disease and without recent disease progression.

- VEGF inhibitors (ranibizumab, aflibercept) are not recommended if there is permanent structural damage to the central fovea or if lesion size is 12 disc areas or greater.
- Treatment with VEGF inhibitors should only be continued for patients who demonstrate a response to therapy. Discontinue treatment if there is persistent deterioration in visual acuity, or identification of anatomical changes in the retina which indicate inadequate response to therapy or that functional improvement is unlikely.
- Photodynamic therapy and intravitreal corticosteroids are not recommended in combination with VEGF inhibitors.

After review, 4 guidelines were excluded due to poor quality.[12,14-16]

New Formulations or Indications:
In 2017, ranibizumab received an expanded indication for use in diabetic retinopathy for patients with or without diabetic macular edema.[17] Approval was based on 2 RCTs which evaluated ranibizumab to sham injection and one RCT comparing ranibizumab to panretinal photocoagulation. Two of the studies were used for FDA-approval in patients with diabetic macular edema and have been evaluated previously. The majority of patients enrolled in these studies had non-proliferative diabetic retinopathy (62%) and 20% of patients had a prior panretinal photocoagulation treatment.[17] The proportion of patients with a 3-step improvement in the ETDRS-Diabetic Retinopathy Severity Scale (DRSS) was evaluated at 24 months. The ETDRS-DRRS evaluates disease severity based on location of microaneurysms, venous beading, hemorrhage, neovascularization, and other intraretinal abnormalities. Patients are categorized into 13 disease severity levels with scores ranging from no retinopathy (score of 10) to severe non-proliferative diabetic retinopathy (score of 53) to advanced proliferative diabetic retinopathy (score of 85).[18] While the scale is non-linear, evidence demonstrates an increased risk of progression to proliferative retinopathy with higher levels of disease.[18] In patients with concomitant diabetic macular edema, more patients treated with ranibizumab had a 3-step improvement from baseline compared to sham injection at 24 months (estimated treatment differences of 15% (95% CI 7 to 22%) and 9% (95% CI 4 to 14%) for each trial).[17] Subgroup analyses based on age, baseline BCVA, disease severity, or prior treatments were consistent with the overall population.[17] One study (n=394) compared ranibizumab to panretinal photocoagulation in patients with or without macular edema.[17] The majority of patients enrolled had proliferative diabetic retinopathy (50% with mild-moderate; 37% with high-risk).[17] Approximately 78% of enrolled patients did not have concomitant macular edema present at baseline.[17] Baseline ETDRS-DRSS severity ranged from 20 to 85.[17] The primary outcome for this trial was mean change in BCVA at 2 years. Results of this study at 2 years indicate ranibizumab was noninferior to panretinal photocoagulation (difference 2.2 letters; 95% CI, -0.5 to 5.0).[19] FDA-approval was based on a secondary subgroup analyses indicating there was no difference in ETDRS-DRSS severity upon comparison of patients with or without macular edema. At 24 months, the proportion of patients with a 3-step improvement from baseline in ETDRS-DRSS was 32% (95% CI 17% to 46%) for patients with baseline macular edema compared to 28% (95% CI 21% to 36%) in patients without macular edema.[17]

In 2019, aflibercept received and expanded indication in a similar population of patients with diabetic retinopathy. Approval was based on data from the same trials used for FDA approval in diabetic macular edema and was supported by additional data from the PANORAMA trial. The PANORAMA trial enrolled patients with non-proliferative diabetic retinopathy and compared aflibercept (dosed every 8 or 16 weeks) to sham injection. The proportion of patients who had a 2 or more step improvement in the ETDRS-DRSS was evaluated at 24 and 52 weeks. At 24 weeks, both treatment groups had a greater proportion of patients with a 2-step improvement from baseline compared to placebo (adjusted difference of 52%; 95% CI 45% to 60%).[20] Significantly more patients at 52 weeks had a 2-step improvement when administered aflibercept every 8 weeks (80%) compared to placebo (15%; adjusted difference of 65%; 95% CI 56 to 74).[20]

New FDA Safety Alerts:
No new FDA safety alerts identified.

Randomized Controlled Trials:
A total of 258 citations were manually reviewed from the initial literature search. After further review, all other citations were excluded because of wrong study design (e.g., observational or post-hoc analyses), comparator (e.g., no control, placebo-controlled, or non-pharmacologic control), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

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

Clinical Efficacy:
FDA approval for brolucizumab was primarily based on results from 2 phase 3 studies (HAWK and HARRIER) with supporting clinical evidence from a phase 2B study.[6,21] HAWK and HARRIER were multicenter, randomized non-inferiority trials evaluating efficacy of brolucizumab compared to aflibercept.

Loading doses of brolucizumab were administered through week 16 with subsequent maintenance doses administered every 8 or 12 weeks based on the disease activity of the patient. Disease activity was assessed based on changes in BCVA and/or new or worsening intraretinal fluid or intraretinal cysts.[6] However, it is unclear whether the criteria used to evaluate disease activity would accurately identify patients needing more frequent treatment. Other clinical trials using similar measures have failed to differentiate between patients needing additional treatment based on final visual acuity tests. Overall, the trial was well designed with only small differences in baseline characteristics. While use of sham injection techniques may increase risk of performance and detection bias, it is less likely to impact objective measures of visual function. Attrition was overall similar between groups. Patients were on average 76 years of age and had a mean BCVA of 60 letters (approximately 20/63 on the Snellen chart).[6] Other disease characteristics are listed in **Table 2**.

In both HAWK and HARRIER, brolucizumab 6 mg was non-inferior to aflibercept for the primary outcome of mean change in BCVA at 48 weeks.[6] The mean difference between treatments was -0.2 letters (95% CI -2.1 to 1.8) for HAWK and -0.7 letters (95% CI -2.1 to 1.0) for HARRIER.[6] The pre-specified non-inferiority margin was defined as a lower limit of -4 letters for BCVA corresponding to a difference of less than one line on the ETDRS chart.[6] Secondary clinical outcomes including mean change in BCVA at 36-48 weeks, and proportion of patients gaining 15 or more letters supported these findings. Subgroup analyses were conducted based on age and baseline BCVA. Results were overall consistent for all subgroups. Only one subgroup (patients with a BCVA of 55 letters or less on the ETDRS chart) failed to meet the prespecified non-inferiority margin.[6]

Secondary anatomic outcomes of disease activity included assessment of CST, presence of subretinal or intraretinal fluid and disease activity at week 16 were tested for superiority based upon a pre-specified analysis.[6] Disease activity was defined as 1) decrease in BCVA of 5 or more letters 2) new or worsening intraretinal cysts or fluid or 3) decrease in BCVA of 3 or more letters and CST increase of at least 75 µm.[6] Often anatomic changes precede visual acuity changes and may serve as an early marker for worsening disease. Brolucizumab 6 mg had improved CST at week 16 (MD of -27.8 µm; 95% CI -45.1 to -10.5 and -40.2 µm; 95% CI -58.9 to -21.6) and presence of subretinal or intraretinal fluid at week 48 (-13.5%; 95% CI -20.7 to -6.1% and 18.1%; 95% CI -24.9 to -11.8%) compared to aflibercept in both trials.[6] Similarly, more patients had reduced disease activity at 16 weeks upon comparison of brolucizumab 6 mg and aflibercept 2 mg every 8 weeks (24% vs. 34%; MD -14.5%; 95% CI -17.1% to -3.5% for HAWK and 23% vs. 32% MD -9.5%; 95% CI -15.8% to -3.1% for HARRIER, respectively).[6] The clinical

significance of these anatomic findings is unclear as there is no consensus on whether CST correlates with functional outcomes. However, these results provide supporting evidence for brolucizumab for treatment of neovascular AMD.

At this time, long-term efficacy, comparison to other treatments for neovascular AMD, and efficacy for other ocular indications remain unknown. There are ongoing clinical trials to assess efficacy of brolucizumab in patients with DME and RVO as well as trials to assess other alternative dosing regimens.

Clinical Safety:
A total of 1088 patients were included in the safety analysis conducted by the FDA.[7] Of these patients, 730 had received the FDA-approved dose of 6 mg.[7] Common adverse events occurring in more than 5% of patients treated with brolucizumab included blurred vision, cataracts, conjunctival hemorrhage, vitreous floaters and eye pain.[7] Overall, occurrence of adverse events was similar to aflibercept, though incidence of cataracts was numerically higher in patients treated with aflibercept (11%) compared to brolucizumab (7%).[7] Labeling is consistent with other VEGF inhibitors and includes contraindications for patients active intraocular inflammation or periocular infection.[7] Warnings which are consistent with other VEGF inhibitors include endophthalmitis, retinal detachment, increased intraocular pressure, and thrombotic events.[7] Additionally brolucizumab had warnings for retinal vasculitis and retinal vascular occlusion which have been reported and typically occur in the presence of intraocular inflammation. In phase 3 trials, incidence of serious ocular adverse events were infrequent (1-3%) and similar between groups.[6] Similarly, there were no statistical differences in rates of serious systemic adverse events compared to aflibercept and events were numerically higher with aflibercept treatment in both trials.[6] Only 1-3% of patients discontinued treatment due to adverse events. Thrombotic events documented over 96 weeks of treatment were 4.5% with brolucizumab compared to 4.7% of patients treated with aflibercept.[7] Thrombotic events thought to be associated with VEGF inhibitor administration can include nonfatal stroke, nonfatal myocardial infarction, or vascular death.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual Function or Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Best corrected visual acuity (BCVA)

Table 1. Pharmacology and Pharmacokinetic Properties.[7]

Parameter	
Mechanism of Action	Brolucizumab is a VEGF inhibitor which binds to VEGF-A isoforms preventing interaction with VEGF receptors and limiting endothelial cell proliferation, neovascularization and vascular permeability.
Oral Bioavailability	NA
Distribution and Protein Binding	Mean Cmax of 49 ng/mL (range 4 to 548 ng/mL) at 24 hours post-dose; no accumulation was observed in most patients after repeated dose administration at 4 weeks
Elimination	Exact excretion is unknown, but it is expected to undergo target-mediated disposition at VEGF receptors or passive renal excretion
Half-Life	Mean 4.4 days (SD 2.0) after a single dose
Metabolism	Exact metabolism is uncharacterized; free antibody is expected to undergo proteolysis

Abbreviations: Cmax = maximum serum concentration; NA = not applicable; ng/mL = nanograms per milliliter; SD = standard deviation; VEGF = vascular endothelial growth factor

Table 2. 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. Dugel, et al.[6] HAWK DB, MC, AC, phase 3, RCT Duration: 2 years	1. brolucizumab 3 mg 2. brolucizumab 6 mg 3. aflibercept 2 mg Aflibercept administered at weeks 0, 4, 8 and every 8 weeks thereafter Brolucizumab administered at weeks 0, 4, 8 and every 12 weeks thereafter. If disease activity was identified after loading period (week 16), dose was increased to every 8 weeks. About 50% of patients maintained dose every 12 weeks throughout the study.	Demographics: - Mean BCVA: 60.6 letters - BCVA ≥71 letters 1. 31% 2. 28% 3. 25% - Mean age: 76.5 - Female: 56% - White: 81%; Asian: 15% - Occult CNV: 58% - Predominately classic CNV: 32% - Mean CST: 462 mm - CST ≥400 mm 1. 56% 2. 56% 3. 59% - Subretinal fluid present: 69% - Subretinal hemorrhage present: 1. 11.5% 2. 15% 3. 14.5% Key Inclusion Criteria: - Age ≥ 50 years - Untreated neovascular AMD - CNV lesions in the central subfield (1mm from the foveal center) - CNV lesions for >50% of total lesion area - Intraretinal or subretinal fluid affecting the central subfield - BCVA of 78 to 23 ETDRS letters (Snellen chart of ~20/32 to 20/400) Key Exclusion Criteria: - Fibrosis, subretinal blood, or geographic atrophy in the central subfield or for ≥50% of the total lesion area - Other current eye conditions (retinal tears, vitreous hemorrhage, IOP ≥ 25 mmHg, infection or inflammation) - Prior therapy for AMD including recent use of VEGF inhibitors, surgery or laser treatment - History of intraocular surgery within prior 90 days, prior vitrectomy,	ITT: 1. 360 2. 361 3. 361 PP: 1. 325 2. 328 3. 312 Attrition: 1. 31 (9%) 2. 37 (10%) 3. 46 (13%)	Primary Endpoint: Change in mean BCVA (week 48) 1. 6.1 (SE 0.69) 2. 6.6 (SE 0.71) 3. 6.8 (SE 0.71) 1 vs. 3: -0.6 (95% CI -2.5 to 1.3); p<0.001 for NI 2 vs. 3: -0.2 (95% CI -2.1 to 1.8); p<0.001 for NI Secondary Endpoints: Change in averaged BCVA (week 36-48) 1. 6.2 (SE 0.67) 2. 6.7 (SE 0.68) 3. 6.7 (SE 0.68) 1 vs. 3: -0.5 (95% CI -2.4 to 1.3); p<0.001 for NI 2 vs. 3: 0 (95% CI -1.9 to 1.9); p<0.001 for NI BCVA gain of ≥ 15 letters 1. 25.2% 2. 33.6% 3. 25.4% p-value NR BCVA loss of ≥ 15 letters 1. 5.9% 2. 6.4% 3. 5.5% p-value NR	NA for all	DC due to AE 1. 8 (2%) 2. 11 (3%) 3. 8 (2%) Ocular AE 1. 175 (49%) 2. 179 (50%) 3. 170 (47%) Ocular SAE 1. 5 (1.4%) 2. 11 (3.1%) 3. 3 (0.8%) Non-ocular SAE 1. 47 (13.1%) 2. 47 (13.1%) 3. 68 (18.9%) Arterial thrombo-embolic event 1. 11 (3.1%) 2. 6 (1.7%) 3. 10 (2.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Adequate randomization and allocation concealment via interactive response technology. Average BVCA and CST was similar between groups, but BVCA≥71 letters was less frequent in aflibercept group which may bias results in favor of treatment and CST≥400 mm was slightly more frequent in aflibercept group which may provide a more conservative treatment effect. Performance Bias: LOW. Use of similar dosing regimen up to 16 weeks only. After week 16, sham placebo injections were administered to maintain blinding. Patient, sponsor, central reading centers and providers involved in monitoring, reviewing, or obtaining clinical evaluations were masked to treatment. Administering providers were not masked to treatment. Detection Bias: LOW. Providers involved in monitoring, reviewing, or obtaining clinical evaluations were masked to treatment. Masked investigator assessed disease activity. Attrition Bias: LOW. Overall attrition was low and slightly more frequent with aflibercept. Analysis performed with both PP and ITT using LOCF or observed data based on mixed-model repeated measures analysis for missing data. Reporting Bias: LOW. Pre-specified hierarchical testing method used to evaluate non-inferiority then superiority. Other Bias: UNCLEAR. Sponsor involved in writing draft. All except one author had financial disclosures related to industry. **Applicability**: Patient: Baseline characteristics consistent with expected AMD population. Intervention: FDA-approved dose of brolucizumab is 6 mg monthly for 3 doses then 6 mg every 8-12 weeks. Comparator: FDA-approved regimen of aflibercept every 8 weeks was used. While brolucizumab maintenance dose was adjusted based on disease activity, aflibercept dose was not. In general, there

		penetrating keratoplasty, panretinal photocoagulation - Corticosteroid eye drops in the prior 6 months - ≥30 days of systemic corticosteroids within the prior 90 days (low stable doses permitted) - Stroke or MI in the prior 90 days or blood pressure > 160/100 mmHg						were no differences in efficacy of monthly vs. every 8 week injections of aflibercept in trials. However, labeling for aflibercept indicates that some patients may benefit from more frequent monthly dosing. Outcomes: Changes of BCVA appropriate to evaluate visual changes in AMD. Setting: New Zealand, Israel, Australia, Japan, North, Central, and South America from December 2014 to May 2016. Proportion of patients from the United States was not reported.
2. Dugel, et al.[6] HARRIER DB, MC, AC, phase 3, RCT Duration: 2 years	1. brolucizumab 6 mg 2. aflibercept 2 mg See HAWK for dosing regimens	Demographics: - Mean BCVA: 61.2 letters - Mean age: 75 years - Female: 57% - White: 92% - Type of CNV - Occult: 50% - Predominately classic: 40% - Mean CST: 469.5 mm - CST ≥400 mm 1. 60% 2. 65% - Subretinal fluid present: 1. 68% 2. 73% - Intraretinal hemorrhage present: 1. 28% 2. 18% Key Inclusion Criteria: See HAWK Key Exclusion Criteria: See HAWK	ITT: 1. 372 2. 371 PP: 1. 351 2. 341 Attrition: 1. 25 (7%) 2. 24 (6%)	Primary Endpoint: Change in mean BCVA (week 48) 1. 6.9 (SE 0.61) 2. 7.6 (SE 0.61) -0.7 (95% CI -2.1 to 1.0); p<0.001 Secondary Endpoints: Change in averaged BCVA at weeks 36-48 1. 6.5 (SE 0.58) 2. 7.7 (SE 0.58) -1.2 (95% CI -2.8 to 0.5); p<0.001 for NI BCVA gain of ≥ 15 letters 1. 29.3% 2. 29.9% p-value NR BCVA loss ≥ 15 letters 1. 3.8% 2. 4.8% p-value NR	NA for all	DC due to AE 1. 12 (3%) 2. 4 (1%) Ocular AE 1. 122 (33%) 2. 119 (32%) Ocular SAE 1. 9 (2.4%) 2. 4 (1.1%) Non-ocular SAE 1. 35 (9.5%) 2. 43 (11.7%) Arterial thrombo-embolic event 1. 6 (1.6%) 2. 8 (2.2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See HAWK. Baseline characteristics mostly balanced. There were slight differences between groups in patients with CST ≥400 mm, intraretinal hemorrhage, and subretinal fluid. Performance Bias: LOW. See HAWK Detection Bias: LOW. See HAWK Attrition Bias: LOW. See HAWK. Overall attrition was low and similar between groups. Reporting Bias: LOW. See HAWK. Other Bias: UNCLEAR. See HAWK **Applicability**: Patient: See HAWK. Intervention: See HAWK. Comparator: See HAWK. Outcomes: See HAWK. Setting: Europe, Middle East, Asia, and Russia. Enrollment dates between June 2105 and April 2016.

Abbreviations [alphabetical order]: AC = active controlled; AE = adverse event; AMD = age-related macular degeneration; ARR = absolute risk reduction; BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascular; CST = central subfield thickness; DB = double blind; DC = discontinuation; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NI = noninferiority; NNT = number needed to treat; NR = not reported; PP = per protocol; RCT = randomized controlled trial; SE = standard error; SAE = severe adverse event.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bevacizumab	AVASTIN	VIAL	intravenous	Y
aflibercept	EYLEA	SYRINGE	intraocular	N
aflibercept	EYLEA	VIAL	intraocular	N
pegaptanib sodium	MACUGEN	SYRINGE	intraocular	N
ranibizumab	LUCENTIS	SYRINGE	intraocular	N
ranibizumab	LUCENTIS	VIAL	intraocular	N

Appendix 2: Abstracts of Comparative Clinical Trials

None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 09, 2020

1	exp bevacizumab/ or exp ranibizumab/	13307
2	aflibercept.mp.	2032
3	brolucizumab.mp.	20
4	pegaptanib.mp.	628
5	exp vascular endothelial growth factors/	53160
6	1 or 2 or 3 or 4 or 5	62378
7	exp Retinal Degeneration/	41253
8	exp Retinal Diseases/	127979
9	7 or 8	127979
10	6 and 9	8152
11	limit 10 to (english language and humans)	6819
12	limit 11 to yr="2017 -Current"	1497
14	limit 12 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	258

Appendix 4: Prescribing Information Highlights

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

BEOVU® (brolucizumab-dbll) injection, for intravitreal injection
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
BEOVU is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three doses, followed by one dose of 6 mg (0.05 mL) every 8-12 weeks (2).

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 6 mg/0.05 mL solution for intravitreal injection in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).
- Hypersensitivity (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.2).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with macular edema
Intervention	Drugs in **Appendix 1**
Comparator	Drugs in **Appendix 1**
Outcomes	Improvement in symptoms (e.g., visual acuity), function, quality of life, mortality, serious adverse events, or withdrawals due to adverse events
Setting	Outpatient

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *3/17 (SS)*
Implementation: *TBD*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Drug Class Literature Scan: Attention Deficit Hyperactivity Disorder (ADHD)

Date of Review: August 2020

Date of Last Review: May 2019
Literature Search: April 2018 – April 2020

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

Conclusions:

- This literature scan identified 2 systematic reviews [1-2], 3 new clinical practice guidelines [3-5], 3 new drug formulations [6-8], 1 expanded drug indication [9], 1 United States Food and Drug Administration (FDA) guidance document [10], and 1 FDA drug safety labeling update. [11] The identified literature supports current policy for attention deficit hyperactivity disorder (ADHD) drugs.
- A Cochrane systematic review of randomized controlled trials of amphetamine for ADHD in adults found an increased proportion of patients who withdrew from treatment due to any adverse events (e.g., insomnia, hypertension, or palpitations/tachycardia) compared to placebo (Relative Risk (RR) 2.69, 95% CI 1.64 to 4.42).[1]
- A Cochrane systematic review of randomized controlled trials (RCTs) of pharmacological treatments for ADHD in children with comorbid tic disorders found low quality evidence that ADHD drugs have not consistently been shown to reduce tic severity.[2] No difference was found in the effectiveness of ADHD agents for the reduction of ADHD symptom severity due to high heterogeneity among the studies.[2]
- The National Institute for Health and Care Excellence (NICE) amended their guideline on ADHD diagnosis and management to specify that an electrocardiogram is not needed before starting stimulants, atomoxetine or guanfacine if the patient's cardiovascular history and examination are normal and the person is not on any medication that increases cardiovascular risk.[3]
- The American Academy of Pediatrics updated guidelines for the management of ADHD in children ages 4 to 17 years made the following key recommendations: primary care clinicians should screen for comorbid conditions such as anxiety, depression, and substance use (Grade B, strong recommendation); management of ADHD should employ a chronic care model and medical home (Grade B, strong recommendation); evidence-based parent training in behavior management (PTBM) and/or behavioral classroom interventions should be used as first-line treatment for preschool-aged children (Grade A, strong recommendation for PTBM); use of FDA-approved medications combined with PTBM and behavioral interventions for elementary, middle school-aged children, and adolescents (Grade A, strong recommendation for medications; Grade A, strong recommendation for training and behavioral treatments for ADHD with family and school).[4]
- The Society for Developmental and Behavioral Pediatrics (SDBP) published guidelines to provide direction for assessment and treatment of children and adolescents with complex ADHD. Recommendations were similar in the American Academy of Pediatrics guideline, which emphasizes a comprehensive ADHD evaluation and management by a qualified specialist, use of evidence-based behavioral and educational interventions, and lifelong care and monitoring for ADHD and comorbidities (all quality of evidence grade B, strong recommendation), as well as use of appropriate evidence-based pharmacological treatments and strategies (evidence quality grade C to B, recommendation). [5]

Author: David Engen, PharmD

- No significant trends were noted in diagnoses of ADHD, narcolepsy, or substance abuse/dependence for Oregon Health Plan (OHP) Fee-for-Service (FFS) patients prescribed ADHD medications listed in Appendix 1.
- There is insufficient evidence that one ADHD drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities.

Recommendations:
- No changes to the current PDL.
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy
Prior reviews have found evidence to support that stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo. Comparisons between different formulations (immediate release [IR] vs. extended release [ER]) within this class have not demonstrated consistent differences. In addition, there is insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults. The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low-quality evidence suggests any differences in harms between various ADHD agents.[12]

To ensure safe and appropriate use within the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Safety edits are in place to ensure that medication use reflects best practices. Any request for a non-preferred agent or for an agent that exceeds the age or quantity limit requires consultation with a specialist prescriber such as a psychiatrist or other mental health specialist. Preferred agents within the ADHD class include atomoxetine, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine dimesylate, and methylphenidate. Three of the medications within the ADHD class are part of the mental health carve-out and are exempt from traditional prior authorization (PA) requirements: atomoxetine, clonidine, and guanfacine. All medications, regardless of PDL status, may be subject to clinical PA criteria to address any safety concerns or to ensure medically appropriate use.

OHP FFS Utilization Summary
In the OHP FFS population during the third quarter of 2019, utilization of the preferred, voluntary, and non-preferred agents in this class were about 50%, 46%, and 4%, respectively.

In a previous review, medically appropriate use was analyzed in both children and adult patients with a paid FFS claim for at least one agent from the ADHD class from 7/1/2017 to 6/30/2018.[13] Patients were included if they had a minimum of 75% OHP eligibility in the year prior to the first ADHD claim and a diagnosis of interest present within the year prior to the ADHD claim.[14] The diagnoses of ADHD and narcolepsy were searched based on their FDA-approved indications while a diagnosis for substance abuse, substance dependence, or drug poisoning was also searched due to the high potential for abuse and dependence of ADHD drugs.[13] A recent search with the same inclusion criteria was conducted in OHP patients from 4/1/2019 to 3/31/2020. Results from the query are outlined in **Table 1**.

Table 1. OHP FFS Utilization of ADHD Drugs by Selected Diagnoses.

Patient Age	Diagnosis	ICD-10 codes	Number of unique patients with a paid FFS claim for ≥1 medication in the ADHD class (%)		% Change
			2017-2018[14]	2019-2020	
Patients <18 years			**7,161**	**8,032**	
	ADHD	F90.x	5,589 (78.0%)	6,298 (78.4%)	↑ 0.4%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	2 (0.0%)	3 (0.0%)	No change
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,571 (21.9%)	1,731 (21.6%)	↓ 0.3%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	185 (2.6%)	230 (2.9%)	↑ 0.3%
	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	13 (0.2%)	19 (0.2%)	No change
Patients ≥18 years			**3,439**	**3,764**	
	ADHD	F90.x	2,197 (63.9%)	2,358 (62.6%)	↓ 1.3%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	15 (0.4%)	27 (0.7%)	↑ 0.3%
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,232 (35.8%)	1,388 (36.9%)	↑ 1.1%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	985 (28.6%)	1,039 (27.6%)	↓ 1.0%
	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	17 (0.5%)	20 (0.5%)	No change

The 2019-2020 analysis showed a 12% increase in the number of unique patients with at least 1 paid FFS claim for an ADHD medication. However, the proportion of patients with a diagnosis of ADHD has remained consistent in both the adult and pediatric populations compared to the 2017-2018 claims data (about 78% and 64%, respectively). There were no meaningful changes in the number of patients diagnosed with narcolepsy, substance abuse or dependence, and poisonings. Since both reviews were based on claims data, there were limitations in the ability to directly connect the medical diagnosis with the ADHD medication pharmacy claims.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and

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

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

New Systematic Reviews:

In August 2018, the Cochrane Collaboration published a systematic review of the efficacy and safety of amphetamine in adults with ADHD.[1] The review included 19 studies (N=2521) of dexamphetamine, lisdexamphetamine, or mixed amphetamine salts at various strengths and doses compared to placebo or active intervention.[1] All studies had a length of treatment from 1 to 20 weeks (mean 5.3 weeks) with short-term follow-up and were considered to have unclear or high risk of bias.[1] Amphetamine efficacy was compared to other pharmacologic agents in 3 studies (n=137) and included either guanfacine, modafinil, or paroxetine.[1] Primary outcomes were measured with the standardized ADHD Rating Scale-IV by either clinicians or patients. The ADHD Rating Scale-IV is an 18-item questionnaire that uses a 4-point Likert scale to record the frequency and severity of ADHD symptoms based on DSM-IV criteria (0 to 54 points total; higher score=worse symptoms).[1] There were no head-to-head comparative studies identified to suggest differences between individual amphetamines or other active treatments in the ability to reduce ADHD symptom severity as measured by the ADHD Rating Scale-IV.[1] However, the authors found low to very low-quality evidence from 17 studies (n=2409) that amphetamines were associated with an increased proportion of patients who withdrew from treatment due to any adverse events such as insomnia, hypertension, or palpitations/tachycardia compared to placebo (RR 2.69, 95% CI 1.64 to 4.42).[1]

In June 2018, the Cochrane Collaboration published a systematic review of pharmacological treatments for ADHD in children with comorbid tic disorders.[2] Eight studies were included in the review (N=510) and included children 18 years of age or younger; 87% were male.[2] The trial sizes ranged from 22 to 148 patients and all had the diagnoses of ADHD and chronic tic disorder (Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder).[2] Several ADHD medications were assessed which included atomoxetine, clonidine, desipramine, dextroamphetamine, guanfacine, and methylphenidate.[2] Most studies were deemed low risk of bias for performance bias (blinding), and low to unclear risk of bias for selection bias (allocation concealment), but two of the studies had high risk of bias in selective reporting.[2] Three of the 8 trials in the review assessed multiple agents while the rest assessed single agents compared to placebo.[2] Study duration was 3 to 22 weeks. All trials were graded as low quality. No meta-analysis was performed due to extensive heterogeneity among the studies.[2]

All studies except for one study of reported improvement in symptoms of ADHD compared to placebo. However, the symptom rating scales employed to measure ADHD severity varied and most trials failed to specify a primary outcome.[2] Therefore, the individual or comparative effectiveness of these agents for improvement of ADHD symptoms could not be adequately assessed. For measurement of tic severity, all included studies used the YGTSS, which is a summation of assessment scores of motor tic, vocal tic, and overall impairment (scale range 0 to 100; higher score=worse symptoms).[2] Three of the studies examined methylphenidate, 2 examined clonidine, and 2 examined desipramine.[2] One of the studies combined the use of 2 agents (methylphenidate plus clonidine).[2] For patients with ADHD and comorbid tic disorder, one study of clonidine monotherapy demonstrated a statistically significant decrease in the YGTSS versus placebo (10.9 points, 98.3% CI 2.1 to 19.7; P = 0.003) while a second study could not find a difference.[2] Of the 3 methylphenidate monotherapy studies, only 1 demonstrated YGTSS reduction at 16 weeks (11.0 points, 98.3%CI 2.1 to 19.8; P = 0.003), one study found no difference on the YGTSS, and the third study reported a worsening of tic severity in week 2 of one of the cohorts (P<0.01).[2] The combination of methylphenidate plus clonidine demonstrated YGTSS

improvements compared to placebo (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003). [2] Only one of the 2 studies with desipramine reported YGTSS score reductions (20 points; P < 0.001; low-quality evidence). [2]

After review, 29 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

National Institute for Health and Care Excellence

In September 2019, NICE published an amendment to their 2018 guideline on ADHD diagnosis and management.[3] The initial recommendation to conduct a baseline assessment of physical health prior to starting medication for ADHD was amended to specify that an electrocardiogram is not needed before starting stimulants, atomoxetine or guanfacine if the patient's cardiovascular history and examination are normal and the person is not on any medication that increases cardiovascular risk.[3] No other updates to the guidelines were identified since the 2018 release.

In 2019, the American Academy of Pediatrics updated their 2011 guideline for the management of ADHD in children ages 4 to 17 years.[4] The update included a review of relevant clinical literature from 2011 through 2016. [4] The new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) had been released within that timeframe and was reflected in the new guideline. [4] Recommendations were made for initial ADHD evaluation, diagnoses, referral guidance, screening for comorbid conditions, care coordination, and age-appropriate treatments. [4] Key recommendations from the guideline is summarized in Table 2.

Table 2. Summary of Key Action Statements for Diagnosing, Evaluating, and Treating ADHD in Children and Adolescents[4] (modified).

Recommendation	Evidence Quality, Strength of Recommendation
Clinician should start ADHD evaluations for children from ages 4 through 17 with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity	Grade B, strong recommendation
Diagnosis of ADHD should meet DSM-5 criteria, including documentation of symptoms and impairment in at least 1 major setting (social, academic, or occupational) by gathering information from parents, guardians, teachers, other school personnel, and mental health clinicians involved in the child's care	Grade B, strong recommendation
The PCC should screen for comorbid conditions, including emotional or behavior types (eg, anxiety, depression, oppositional defiant disorder, conduct disorders, substance use), developmental conditions (eg, learning and language disorders, autism spectrum disorders), and physical conditions (eg, tics, sleep apnea) PCC should initiate treatment of comorbid conditions if experienced; if not, refer patient to an appropriate specialist	Grade B, strong recommendation Grade C, recommendation
Patient management should involve a long-term chronic care/medical home model	Grade B, strong recommendation
Treatment for children ages 4 to 5 years: • Use evidence-based PTBM and/or behavioral classroom interventions as first-line therapy, if available	Grade A, strong recommendation

• Methylphenidate may be considered if PTBM does not show improvement or if a disturbance in functioning is observed but risks of therapy before age 6 should be weighed against harms of treatment delay	Grade B, strong recommendation
Treatment for children ages 6 to 11 years: • Use FDA-approved medications, along with PTBM and/or behavioral classroom intervention	Grade A, strong recommendation
Treatment for children ages 12 to 17 years: • Use FDA-approved medications with the adolescent's assent, along with PTBM and/or behavioral classroom intervention	Grade A, strong recommendation
Clinician should titrate medication doses to achieve maximum benefits with tolerable side effects	Grade B, strong recommendation

Evidence Quality	Evidence Grade	Evidence Interpretation
Level A - well-designed randomized controlled trials or diagnostic studies on relevant population Level B - randomized controlled trials with minor limitations; overwhelmingly consistent evidence from observational studies Level C - observational studies (case-control and cohort design)	Grade A: consistent level A evidence Grade B: consistent level B or extrapolations from level A evidence Grade C: level C evidence or extrapolations from level B or level C evidence	"Strong Recommendation" = benefits of the approach clearly exceed the harms of that approach "Recommendation" = benefits exceed the harms, but the quality of the evidence is not as strong

Abbreviations: PCC = primary care clinician; PTBM = parent training in behavioral management.

A new guideline was released in 2020 by the SDBP to provide direction for assessment and treatment of children and adolescents with complex ADHD.[5] Complex ADHD was defined by age (<4 years or presentation at age >12 years), presence of comorbidities, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment. [5] The SDBP followed the same methodology as the AAP to develop their practice guidelines in order to keep cohesion and consistency with current standards. [5] The recommendations were condensed into 5 key action statements and were assigned an evidence grade:

- implementation of a comprehensive evaluation by a clinician with specialized training (quality of evidence grade B, strong recommendation) [5]
- use of appropriate, comprehensive assessments with verification of pre-existing comorbidities, functional impairments, and developmental deficiencies (quality of evidence grade B, strong recommendation) [5]
- evidence-based behavioral and educational interventions to build knowledge and skills in complex ADHD management (quality of evidence grade B, strong recommendation) [5]
- use evidence-based pharmacological treatments and strategies for management of complex ADHD and associated comorbidities to improve symptoms, function, encourage self-management, and avoid adverse outcomes (quality of evidence grade C to B, recommendation) [5]
- include lifetime patient management and monitoring especially during key developmental transition periods (quality of evidence grade B, strong recommendation). [5]

New Formulations or Indications:

In August 2018, the FDA approved an extended-release (ER) capsule formulation of methylphenidate (Jornay PM®) to treat ADHD in patients 6 years of age and older. The approval was based on 2 clinical trials of pediatric patients 6 to 12 years of age.[6] A full risk of bias and applicability evaluation was unclear as studies used for FDA-approval were not published. Study 1 was as 7-week, phase 3 randomized withdrawal trial. All patients (n=117) received Jornay PM® at flexible doses between 20 mg and 100 mg once each evening for 6 weeks. The open-label phase was followed by a 1-week, double blind, placebo-controlled phase in which patients were randomized to remain on optimized doses of Jornay PM (n=64) or change to placebo (n=53).[6] After the 1 week double-blinded treatment phase, patient response was assessed over 12 hours with the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP). SKAMP is a 13-item, 78-point observer-rated scale (0=normal, 78=maximal impairment) used to evaluate ADHD indicators in the classroom environment such as attention, deportment, work quality, and rule compliance.[6] The study used a model-adjusted average of all post-dose SKAMP-combined scores (SKAMP-C) measured during the 12-hour testing period as the primary endpoint.[6] A statistically significant reduction in the SKAMP-C average score was reported for Jornay PM® compared to placebo (least squares mean difference -5.9 [95% CI -9.1 to -2.7]).[6] Mean baseline scores were not available for comparison.

In study 2, Jornay PM® was evaluated in a 3-week, multicentered, randomized, double-blind, placebo-controlled, parallel-group study in 6 to 12-year old pediatric patients.[6] Patients were randomized to receive Jornay PM® (n=81) at variable doses (40 mg, 60 mg, 80 mg) or placebo (n=80) administered once daily in the evening.[6] Dose and administration times were adjusted by subjects based on tolerability and control of ADHD symptoms. The primary efficacy endpoint was measured with the ADHD-RS-IV (54 points total; 0=no ADHD symptoms, 54=severe symptoms).[6] The intention-to-treat population used for the primary endpoint consisted of all randomized patients who received at least 1 dose of the study drug and at least 1 post-baseline evaluation with the ADHD-RS-IV.[6] At 3 weeks, a statistically significant difference was reported on the ADHD-RS-IV symptom score in the Jornay PM® group compared to the placebo group (24.1 vs 31.2 points, respectively; least-squares mean ADHD RS-IV -7.0 [95% CI -11.4 to -2.7]).[6] Mean baseline ADHD RS-IV scores for Jornay PM® and placebo were 43.5 and 43.1, respectively. Jornay PM® was not studied in this trial at the 20 mg or 100 mg doses.[6]

Treatment emergent adverse events were collected from the start of study treatment up to the safety follow-up assessment (35 days).[6] Adverse reactions that occurred in at least 5% of Jornay PM®-treated pediatric patients and occurred at a greater frequency than placebo are listed in Table 3.[6]

Table 3. Adverse Reactions Reported in the Jornay PM® 3-Week ADHD Study (Study 2).[6]

Adverse Reaction	Jornay PM® (N=81)	Placebo (N=80)
Insomnia	33%	9%
Decreased appetite	19%	4%
Headache	10%	5%
Vomiting	9%	0%
Blood pressure diastolic increased	7%	4%
Nausea	6%	0%
Affect lability/mood swings	6%	1%
Psychomotor hyperactivity	5%	1%

In January 2019, the FDA approved Evekeo ODT®, a new formulation of amphetamine sulfate.[7] The safety and effectiveness of Evekeo ODT® in the treatment of ADHD was established based on the studies of the reference product, immediate-release amphetamine sulfate (Evekeo), under the 505(b)(2) regulatory pathway.[7] Evekeo ODT® is a short-acting orally disintegrating tablet indicated for the treatment of ADHD in pediatric patients 6 to 17 years of age.[7]

The FDA also approved Adhansia XR® (methylphenidate ER) capsules in February 2019 for the treatment of ADHD in patients 6 years and older.[8] Adhansia XR® labeling identified 4 studies used for FDA approval, but a full risk of bias and applicability evaluation was unclear as studies used for FDA-approval were not yet published. Adhansia XR® was first evaluated in 2 double-blind, randomized placebo controlled trials of adult patients between the ages of 18 and 72 years who met the DSM-5 criteria.[8] Study 1 (n=375) evaluated methylphenidate ER at 25 mg, 45 mg, 70 mg, and 100 mg once daily compared to placebo.[8] Patients were titrated over 2 weeks and then assigned a maintenance dose over 2 more weeks.[8] The primary efficacy endpoint was change from baseline in the ADHD-RS-5 (visit 2, week 1) to visit 6 in week 5.[8] Adhansia XR® demonstrated statistically significant improvements only at the 45 mg and 100 mg doses compared to placebo (-7.1 [95% CI -10.8 to -3.4] and -7.9 [95% CI, -11.6 to -4.1], respectively).[8]

In a second Adhansia XR® study, adult patients aged 18 to 58 with ADHD were titrated over 2 to 7 weeks to methylphenidate ER 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or 100 mg given orally once daily in an open-label phase.[8] In the second crossover phase, patients were randomized to either 1 week of study drug followed by placebo or 1 week of placebo followed by study drug.[8] The primary efficacy endpoint studied was the change in the Permanent Product Measure of Performance Total (PERMP-T) averaged across all timepoints in a simulated adult workplace environment (AWE). The PERMP-T score measures the number of correctly answered math problems attempted and answered correctly.[8] Higher PERMP scores indicate less severe ADHD symptoms. Efficacy assessments were calculated at pre-dose, and 1, 2, 5, 8, 11, 14, and 16 hours post-dose during the AWE sessions.[8] The full analysis population (N=46) included all randomized subjects who received any amount of study medication for at least one post dose time point. Adhansia XR demonstrated a statistically significant improvement in PERMP-T score compared to placebo at most post-dose time points (mean difference 26.8 [95% CI, 15.2 to 38.4]) but not at 14 hours post-dose.[8]

Adhansia XR® was also studied in 2 additional RCTs of pediatric patients with ADHD (n=354).[8] Study 3 was a 4-week, randomized, double-blind, placebo-controlled study in pediatric patients aged 12-17 years who met DSM-5 ADHD criteria.[8] Patients were randomized to once-daily methylphenidate ER 25 mg, 45 mg, 70 mg, 85 mg, or placebo groups.[8] As in study 1, the primary efficacy endpoint was change from baseline in the ADHD-RS-5 total score from baseline (week 1) to Visit 6. At visit 6, Week 5, Adhansia XR demonstrated statistically significant changes from baseline on the ADHD-RS-5 total score only for the 45 mg and 70 mg doses compared to placebo (-5.4 [95% CI, -9.2 to -1.6] and -5.2 [95% CI, -9 to -1.4] respectively), but not at the other doses.[8]

In study 4, Adhansia XR® was evaluated in 6 to 12-year old patients with ADHD (n=147).[8] Patients were randomized to either methylphenidate ER 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or placebo.[8] The trial consisted of a 6-week, open-label, flexible dosing period with a 1-week randomized treatment phase with an optimized patient dose.[8] Most patients were optimized to a dose between 45 and 55 mg.[8] After the randomized phase, patients were evaluated at pre-dose and 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose on simulated classroom day using the SKAMP-C.[8] The primary efficacy endpoint measured was change in the mean SKAMP-CS, averaged across the 8 timepoints on the analog classroom day.[8] Through all post-dose laboratory classroom hours, Adhansia XR was reported to show a statistically significant improvement in SKAMP-C score compared to placebo (Placebo-subtracted difference, -8.6 [95% CI, -10.6 to -6.6]).[8]

The most common adverse reactions, with incidence greater than or equal to 5% and at rate at least twice the frequency of placebo, reported in Adhansia XR-treated pediatric patients (6 to 12 years of age) were decreased appetite (35%), insomnia (10%), upper abdominal pain (15%), affect lability (13%), nausea or vomiting (13%), decreased weight (12%), insomnia (10%), irritability (10%), and headache (10%).[8] In patients 12 to 17 year of age, the most common adverse reactions for Adhansia XR®-treated patients compared to placebo were decreased appetite (20% vs. 0%, respectively), decreased weight (7% vs. 0%,

respectively), and insomnia (6% vs. 1%, respectively).[8] Similar adverse effects and rates were observed in Adhansia XR®-treated adults compared to placebo, but with additional reports of dry mouth (9% vs 4%, respectively).[8] Adhansia XR® has an FDA boxed warning for risk of abuse and dependence.[8]

In February 2019, a formulation of amphetamine 2.5 mg/ml oral suspension (Dyanavel XR®) received FDA approval for an expanded indication in patients 6 years of age and older.[9] Previously, the FDA labeling authorized use of Dyanavel XR® for the treatment of ADHD in children ages 6 to 17 years old.[9] The FDA, however, deferred the submission of a pediatric study for ages 4 to 5 years until additional safety or effectiveness data have been collected.[9]

New FDA News:

In May 2019, the FDA released a draft guidance document to provide a general framework of recommendations to sponsors for the streamlined development of stimulant drugs for treatment of ADHD in pediatric and adult patients.[10] The guidance did not address development programs for nonstimulant drugs.[10] The guidance specifically provided advice for drug manufacturers to identify mechanisms to help reduce patient exposure to potential harms in methylphenidate and amphetamine 505(b)(2) drug development programs through extrapolation of data from safety and efficacy studies.[10] The recommendations also include criteria to determine when extrapolation of pharmacokinetic data is appropriate and when clinical trials would be necessary, especially in pediatric populations.[10] Guidance was given regarding safety monitoring parameters to track adverse reactions such as increased blood pressure and heart rate, appetite suppression, delayed growth, and insomnia.[10] The draft guidance document was distributed for comment purposes only.[10]

New FDA Safety Alerts:

Table 4. Description of New FDA Safety Alerts[11]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Methylphenidate hydrochloride	Aptensio XR®	6/14/2019	Use in Specific Populations	Due to high rates of adverse reactions, most notably weight loss, the benefits of using APTENSIO XR do not outweigh the risks in pediatric patients 4 to <6 years of age.

References:

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http://www.orpdl.org/durm/meetings/meetingdocs/2017_09_28/archives/2017_09_28_ADHD_ClassUpdate.pdf. Accessed April 10, 2020.
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Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y
dexmethylphenidate HCl	FOCALIN	TABLET	Y
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y
methylphenidate	DAYTRANA	PATCH TD24	Y
methylphenidate HCl	METADATE CD	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y
methylphenidate HCl	RITALIN	TABLET	Y
clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V
clonidine HCl	KAPVAY	TAB ER 12H	V
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V
guanfacine HCl	INTUNIV	TAB ER 24H	V

amphetamine	ADZENYS ER	SUS BP 24H	N
amphetamine	AMPHETAMINE	SUS BP 24H	N
amphetamine	DYANAVEL XR	SUS BP 24H	N
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N
amphetamine sulfate	EVEKEO	TABLET	N
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N
dextroamphetamine sulfate	DEXEDRINE	TABLET	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N
dextroamphetamine sulfate	ZENZEDI	TABLET	N
dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	N
methamphetamine HCl	DESOXYN	TABLET	N
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N
methylphenidate HCl	RITALIN LA	CPBP 50-50	N
methylphenidate HCl	JORNAY PM	CPDR ER SP	N
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N
methylphenidate HCl	METHYLIN	SOLUTION	N
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N
methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N
methylphenidate HCl	CONCERTA	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N
methylphenidate HCl	RELEXXII	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET ER	N

Appendix 2: New Comparative Clinical Trials

A total of 110 citations were manually reviewed from the initial literature search. After further review, all were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to April 06, 2020
1 atomoxetine.mp. or Atomoxetine Hydrochloride/ 1769
2 dexmethylphenidate.mp. or Dexmethylphenidate Hydrochloride/ 89
3 dextroamphetamine.mp. or Dextroamphetamine/ 7133
4 amphetamines.mp. or Amphetamines/ 9374
5 Lisdexamfetamine Dimesylate/ or lisdexamphetamine.mp. /272
6 methylphenidate.mp. or Methylphenidate/ 9138
7 clonidine.mp. or Clonidine/ 18205
8 guanfacine.mp. or Guanfacine/ 1053
9 methamphetamine.mp. or Methamphetamine/ 13302
10 Attention Deficit Disorder with Hyperactivity/ 28208
11 adhd.mp. /24847
12 "Attention Deficit and Disruptive Behavior Disorders"/ 2822
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 /55408
14 10 or 11 or 12 /36855
15 13 and 14 /6213
16 limit 15 to english language /5830
17 limit 16 to humans /4813
18 limit 17 to (yr="2018 -Current" and clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review") /110

Appendix 5: Key Inclusion Criteria

Population	Adult and pediatric patients with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)
Intervention	Drugs in ADHD class (Appendix 1)
Comparator	Drugs in ADHD class (Appendix 1) or placebo if clinically important safety outcomes
Outcomes	Efficacy: symptom improvement, functional capacity, quality of life, time to onset of effectiveness, duration of effectiveness Safety: withdrawals due to adverse events, serious and long term (>12 months) adverse events, misuse/diversion
Timing	Literature from 4/1/18 to 4/1/20
Setting	Outpatient

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

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 and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS		
Indication	**Methylphenidate and derivatives****	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years	Age ≥3 years	Age ≥6 years	Children age 6-17 years only	Children age 6-17 years only
Narcolepsy	Age ≥6 years	Age ≥6 years	Not approved	Not approved	Not approved

See **Table 2 for off-label methylphenidate IR dosing for age ≥ 4 years

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg

CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	Combination therapy not recommended
Age 6-17 years*	1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA 1 CNS Stimulant Formulation (LA or IR) + Clonidine LA
Age ≥18 years**	Combination therapy not recommended

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)
* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5

Approval Criteria		
5. Is the request for an approved FDA diagnosis defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *6/20; 5/19; 9/18 (JP); 5/16; 3/16; 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *11/1/2018; 10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

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Drug Use Evaluation: Immune Globulins

Purpose of the Review:

- Immune globulin (IgG) formulations appear on the top physician assisted drug (PAD) report due to high utilization. Immune globulins are used for many off-label uses without the support of high-quality evidence. This evaluation will determine the number of IgG claims that are used for an approved Food and Drug Administration (FDA) indication or off-label usage. If they are used for an off-label diagnosis, the indication and the evidence supporting that indication will be evaluated.

Research Questions:

- How many IgG claims in the fee-for-service (FFS) population are used for an FDA-approved diagnosis?

Conclusions:

- There were 30 unique patients with a PAD or point of sale pharmacy claim for a drug in the IgG preferred drug list (PDL) class from January 1, 2018 to December 31, 2018. Of those, 17 patients (56.6%) had a claim for an FDA approved indication, 9 (30%) patients with claims for an off-label diagnosis, and 4 (13.3%) patients with no known diagnosis associated with the claim.
- Claims for an FDA-approved indication accounted for 56 claims (54.4%) and 12 (11.7%) claim were for an off-label indication, 35 (34%) of claims were not associated with any indication.
- Immune globulin use in patients with a transplant indication accounted for the largest number of off-label use with 4 patients and 6 claims.
- Ten percent of patients (n=3) had IgG claims for the preferred treatment, GAMUNEX-C (2 patients with an approved indication and 1 patient with an off-label diagnosis).
- Over half of IgG claims are prescribed in concordance with FDA labeling. There are no strong trends in the data that suggest policy changes are necessary at this time.

Recommendations:

- Recommend reanalyzing off-label use annually to inform future restrictions within the class.

Background

There are several types of intravenous IgG (IVIG) formulations, 5 exclusively subcutaneous IgG (SCIG) products, and 1 intramuscular IgG product. Several IVIG products may also be administered subcutaneously. Immune globulin replacement has demonstrated efficacy in multiple outcomes, such as disease improvement, increased functionality, and reduced incidence of infection (**Table 1**).[2] Previous reviews have found no evidence to suggest efficacy differences between IVIG formulations. Products containing high amounts of IgA are associated with a higher number of adverse events, specifically anaphylaxis. Products with a sucrose stabilizer were associated with higher rates of osmotic renal injury than products using a non-sucrose stabilizer. There are not currently any sucrose-based products available in the United States. There is no evidence to suggest efficacy or safety differences between IVIG and SCIG products. Immune

globulins are also commonly used for off-label indications, as monotherapy or in combination with other agents or therapies (e.g., plasma exchange), which is substantiated by limited evidence for certain disease states or insufficient evidence of efficacy for other indications (**Table 2**). A 2014 drug utilization review found that 73% of patients in the Oregon Medicaid fee-for-service (FFS) population had an FDA-approved indication and 24% had an indication supported by efficacy data, suggesting appropriate use of IgG. GAMMAGARD (IgG [Human] 10%) and OCTAGAM (IgG [Human] 5%) were identified in the top 50 FFS PAD medical claims in the second quarter of 2019.

Table 1. FDA-Approved Indications for Immune Globulin Products[2]

Indication
• Primary immunodeficiency
• Immune thrombocytopenia purpura (ITP)
• Multifocal motor neuropathy (MMN)
• B-cell chronic lymphocytic leukemia (CLL)
• Kawasaki syndrome
• Chronic inflammatory demyelinating polyneuropathy (CIDP)

Table 2. Off-label uses for Immune Globulin Products[2,3]

Diagnosis
• Multiple Sclerosis (MS)
• Systemic lupus erythematosus
• Scleroderma
• Myocarditis
• Guillain-Barré syndrome
• Sjogren syndrome
• Dermatomyositis
• Myasthenia gravis (MG)
• Autoimmune thrombocytopenia in pregnancy
• Dermatological auto-immune diseases
• Toxic epidermal necrolysis (TEN) / Stevens-Johnson syndrome (SJS)

A recent Drug Effectiveness Review Project (DERP) review of off-label IgG use in treatment of autoimmune disorders did not find high-quality clinical evidence supporting efficacy for off-label indications.[2] A systematic review of the literature identified 10 trials of IVIG in patients with multiple sclerosis (MS), myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (**Table 3**). No evidence was found for the use of SCIG. The trials were found to be of poor or fair methodological quality. The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

Table 3. Findings from DERP for the Off-Label Use of Immune Globulins

Indication	Findings
Multiple Sclerosis (relapsing-remitting and acute relapse)	- IVIG reduced yearly exacerbation rate (0.59 events per year) compared to placebo (1.61 events per year) (p=0.001) in one trial - Study of IVIG infusion, given every 4-weeks, was not found to be more effective than placebo in the number of relapse-free participants - Combination IVIG and methylprednisolone was not more effective than methylprednisolone alone in preventing relapse
Myasthenia Gravis	- No significant differences were found between IVIG and plasma exchange in the degree of disability
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	- One small (n=27) study found Gammagard and Kiovig (not available in the US) IVIG to have similar efficacy based on the Overall Disability Sum Score
Guillain-Barré Syndrome*	- A single administration study of IVIG and plasma exchange demonstrated similar findings on a validated functional scale - Plasma exchange followed by IVIG had similar efficacy as plasma exchange or IVIG alone based on functional disability

Abbreviations: IVIG – intravenous immunoglobulin
Key: * Not approved for Guillain-Barré Syndrome in the United States

Off-label IgG use was the focus of several Canadian Agency for Drugs and Technology in Health (CADTH) evidence reviews.[3–8,,9] There was no evidence to support the use of IgG for some indications, and mixed or limited evidence for their use in other indications (**Table 3**). Evidence for some indications lacked precision, requiring additional studies to clarify effect. The authors concluded that there was limited evidence to support off-label use of IgG in autoimmune diseases.

Table 3. CADTH Evidence for Off-label Use of Immune Globulin Products[3-7]

Condition	Indication with No Supporting Evidence for Use	Indication for which the Efficacy Evidence is Limited* or May or May not Provide Benefit
Neurological	• Alzheimer disease • Encephalitis • Post-polio Syndrome	• Pediatric Guillain-Barré Syndrome*ǂ • Multiple sclerosis* • Epilepsy • Myasthenia Gravis • Chronic inflammatory demyelinating polyneuropathy
Hematological	• Aplastic anemia • Autoimmune neutropenia • Hyperhemolysis after transfusion • Acquired Hemophilia	• Blood conditions affecting the fetus or newborn*
Autoimmune or Inflammatory	• Dermatomyositis • Myasthenia Gravis • Polymyositis • Kawasaki disease • Sydenham chorea • Acute rheumatic fever cardiac complications	• Systemic lupus erythematosus* • Cardiac outcomes in infants of mothers with antiphospholipid syndrome during pregnancy*

Dermatological	• Stevens-Johnson syndrome – survival benefit	• Stevens-Johnson syndrome – decreased recovery time with high dose* • Bullous pemphigoid* • Polymyositis* • Dermatomyositis*
Recurrent Spontaneous Abortion	• No effect on obstetrical, perinatal, and neonatal outcomes	• Improved live-birth rates in some studies
Solid Organ Transplant Rejection (chronic, antibody mediated rejection)	• No benefit on renal transplant outcomes when given with rituximab	• Improved renal transplant outcomes versus methylprednisolone*

Key: ł Health Canada considers adult Guillain-Barré syndrome as an "on-label" use

Cochrane systematic reviews have not found evidence to support the use of off-label IgG for the following indications: encephalitis[10], epilepsy[11], presumed viral myocarditis in children and adults[12], and suspected or proven infection in neonates. However, IVIG reduced recovery time to a similar extent as plasma exchange (PLEX) in patients with severe forms of Gullain-Barré syndrome (mean difference 0.02; 95% CI, 0.25 to 0.20; moderate strength evidence).[13]

Guidance from the European Academy of Dermatology and Venereology support the use of IVIG in patients with toxic epidermal necrolysis (TEN) despite lack of high-quality evidence due to the severity and rarity of the condition.[14] Additional indications for IVIG recommended by the guidelines are: severe forms of dermatomyositis, severe autoimmune blistering diseases, severe systemic vasculitic syndromes, severe forms of lupus erythematodes, and scleromyxedema. Recommendations were based on consensus of expert opinion and authors had conflicts of interest. Guidance was included due to lack of other sources of high-quality evidence.

<u>American Society of Hematology – 2011 Evidence-based Guidelines for Immune Thrombocytopenia</u>

The American Society of Hematology (ASH) offers guidance on the treatment of immune thrombocytopenia (ITP) in pregnant adults.[1] This guideline is included due to the high number claims in OHP FFS population for off-label use of IgG in patients with ITP in pregnancy. There is insufficient evidence on the management of ITP in pregnant adults. The expert consensus is to treat pregnant adult patients in the same manner as non-pregnant adults. The ASH strongly recommends corticosteroids or IVIG for treatment of ITP in pregnancy based on low quality evidence.[1]

Methods:

Patients of any age were included if they had a paid FFS PAD or pharmacy POS claim for an IgG in the Immune Globulin preferred drug list (PDL) class from January 1, 2018 to December 31, 2018. Diagnoses for FDA-approved and off-label conditions (as defined in **Table 4**) were identified based on the diagnosis submitted on the claim within the study period for patients with an IgG claim. If patients have claims with multiple diagnoses, they may be counted more than once. Claims were classified as new start (no claims for IgG 6 months prior to start of study period) or continuous therapy (any IgG claim 6 months prior to start of study period or multiple claims within the reporting period). Patient demographic data were collected based on the reference claim (the first paid claim for IgG) for the reporting period.

Patients were excluded if they had Medicare crossover claims for an IgG product indicating Medicare Part B coverage.

Table 4. Diagnosis codes of Disease States of Interest

Diagnosis Code (ICD-10)	Disease State
FDA Approved Diagnosis	
D84.9, D80.2, D80.3, D80.4	Primary immunodeficiency, immunoglobulin deficiency
D69.3, D69.4, D69.5, D69.6	Immune thrombocytopenia purpura (ITP)
M30.3	Kawasaki syndrome
G61.82	Multifocal motor neuropathy (MMN)
C91.1, C91.10, C91.11, C91.12	B-cell chronic lymphocytic leukemia (CLL)
G61.81	Chronic inflammatory demyelinating polyneuropathy (CIDP)
Off-label Diagnosis	
G70, G70.0, G70.00, G70.01	Myasthenia gravis (MG)
O99.119	ITP in pregnancy
G35	Multiple sclerosis
M32	Systemic lupus erythematosus
L94, L94.1, M34	Scleroderma
A38.1, A39.52, B26.82, B33.22, B58.81, D86.85, I01.2, I09.0, I40, I41, I51.4, J10.82, J11.82	Myocarditis
G61.0, G65.0	Guillain-Barré syndrome
M35.0	Sjogren syndrome
M33.10	Dermatomyositis
L12.0, L12.3, Q81, L10, L01, H35.06, L95, M05.2	Dermatological auto-immune diseases
L51.2, L51.3, L51.1, L51.3	Toxic epidermal necrolysis (TEN)/ Stevens-Johnson syndrome (SJS)

Results:

The search found 30 patients with claims (4 point of sale [pharmacy] claims and 26 physician administered) for an IgG product in the designated time period. Mean patient age was 24 years, 60% were female, and 63% were white (**Table 4**). Seventy percent of patients were administered IgG in the outpatient hospital setting. Sixty-three percent were new starts and 37% had prior use of IgG. Immune globulin use in distinct patients for an FDA-approved indication was documented in 17 (56.6%) patients, 9 patients (30%) used IgG for an off-label indication, and 4 patients (13.3%) used IgG without a noted diagnosis (**Table 5**). Primary immunodeficiency accounted for 40% of the FDA-approved uses. Solid organ transplant (13.3%) was the most common diagnosis for patients with off-label use. Claims for patients with an FDA-approved diagnosis accounted for 54.4% of all claims in the study period and off-label use accounted for 11.7% of claims. Four patients, all with point of sale claims, had an unknown diagnose and accounted for 34% of all claims in the study period (**Table 5**). Immune globulin utilization was divided between 7 different agents, with GAMMAGARD, FLEBOGAMMA and PRIVIGEN the most commonly prescribed (**Table 6**). There was no utilization for BIVIGAM, CUTAQUIG, CUVITRA, GAMMAKED, GAMMAPLEX, and PANZYGA.

Table 4. Demographics

	Number of Patients (N=30)	Percent
Mean Age: 24 years		
Female	18	60%
Race		
• White	19	63.3%
• Unknown	9	30.0%
• Other	2	6.6%
IgG Product		
• Gammagard liquid (IV or SC)	10	33.3%
• Privigen (IV)	5	16.7%
• Flebogamma (IV)	5	16.7%
• Octagam (IV)	4	13.3%
• Gamunex-C (IV or SC)	3	10.0%
• Hizentra (SC)	2	6.7%
• Hyqvia (SC)	1	3.3%
Prior IgG Use		
• New Start	19	63.3%
• History of IgG	11	36.7%
Indication		
• FDA Approved	17	56.6%
• Off-label use	9	30.0%
• None	4	13.3%
Setting based on claim type*		
- Hospital (Outpatient PAD)	21	70.0%
- Clinic (Professional PAD)	5	16.7%
- Pharmacy POS	4	13.3%

* Patients may be counted more than once if they had claims in multiple settings or claims for multiple diagnoses.

Table 5. Summary of Immune Globulin Use by Diagnosis

Indication	Number of Patients # (%)	Number of Claims	Evidence for Use
Any FDA-approved indication	17 (56.6%)	56 (54.4%)	
Immune thrombocytopenia purpura (ITP)	4 (13.3%)	50	Approved indication
Chronic inflammatory demyelinating polyneuropathy (CIDP)	1 (3.3%)	1	Approved indication
Primary immunodeficiency	12 (40%)	5	Approved indication
Off-label Indication	9 (30.0%)	12 (11.7%)	
Myasthenia gravis (MG)	1 (3.3%)	2	May provide benefit
Transplant	4 (13.3%)	6	Limited evidence of benefit

Asthma	1 (3.3%)	1	Insufficient evidence
Degenerative disease of the nervous system	1 (3.3%)	1	Insufficient evidence
Juvenile dermatomyositits	2 (6.6%)	2	Insufficient evidence
Unknown	4 (13.3%)	35 (34%)	

Table 6. Claims for Immune Globulins According to Diagnosis

	FLEBOGAMMA	GAMMAGARD	GAMUNEX-C	HIZENTRA	HYQVIA	OCTAGAM	PRIVIGEN
Any FDA-approved indication							
Immune thrombocytopenia purpura (ITP)	1	3	1				
Chronic inflammatory demyelinating polyneuropathy (CIDP)		1					
Primary immunodeficiency	13	19	1			16	1
Off-label Indication							
Myasthenia gravis (MG)						2	
Transplant		3	2				1
Asthma						1	
Degenerative disease of the nervous system							1
Juvenile dermatomyositits							2
Unknown		3		29	2		

Table 7. Provider Information for Immune Globulin Claims*

Provider	Number of Patients # (%)	Number of Claims # (%)
Hematology and Oncology	9 (23%)	47 (46.5%)
Pulmonology	1 (2.6%)	3 (3%)
Rheumatology	1 (2.6%)	2 (2%)
Internal Medicine/Family Medicine	1 (2.6%)	1 (1%)
Nurse Practitioner	1 (2.6%)	1 (1%)
Hospital listed as provider	26 (66.7%)	47 (46.5%)

* Patient counts are not unique, as some patients fall under multiple providers

Conclusions:

Fifty-seven percent of IgG claims were used for an FDA-approved indication. Off-label use of IgG accounted for about 30% of claims for the designated time period. Patients with an IgG claim without a diagnosis were point of sale claims, which can be a limitation in obtaining a diagnosis. There is no discernable trend

in prescriber type or type of IgG prescribed. Requiring a diagnosis be applied to IgG claims would inform if administration is used for an appropriate indication. Additional data would help to inform policy decisions in the future.

Limitations:
Inherent limitations to Medicaid claims data:

- Diagnostic accuracy: Diagnoses data based on claims may be inaccurate or incomplete. Diagnoses must be submitted for PAD claims, but are not associated with POS pharmacy claims; therefore, it is difficult to determine the intended indication of the drug.
- Provider Specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designation may not be identified.
- Days of coverage: Estimated number of covered days attempts to approximate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately.
- No diagnosis: It is difficult to draw conclusions of appropriate utilization when 34% of patients with an IgG claim had no associated diagnosis.

References:

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15. Bamford A, Tudor-Williams G, Foster C. Post-exposure prophylaxis guidelines for children and adolescents potentially exposed to HIV. *Arch Dis Child*. 2017;102(1):78-83. doi:10.1136/archdischild-2015-309297

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Prior Authorization Criteria Update: Oncology

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

Table 1. New oncology drugs

Brand Name	Generic Name
TABRECTA	capmatinib
DARZALEX FASPRO	daratumumab and hyaluronidase-fihj
ZEPZELCA	Lurbinectedin
PHESGO	pertuzumab/trastuzumab/haluronidase-zzxf
QINLOCK	ripretinib
RETEVMO	selpercatinib
KANJINTI	trastuzumab-anns
OGIVRI	trastuzumab-dkst
ONTRUZANT	trastuzumab-dttb
HERCEPTIN HYLECTA	trastuzumab-hyaluronidase-oysk
HERZUMA	trastuzumab-pkrb
TRAZIMERA	trastuzumab-qyyp

Recommendation:

- Modify PA to include new, recently approved antineoplastic drugs. Include newly approved biosimilars in the policy.

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

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

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

Approval Criteria

9. All other diagnoses must be evaluated for evidence of clinical benefit.

   The prescriber must provide the following documentation:
   - medical literature or guidelines supporting use for the condition,
   - clinical chart notes documenting medical necessity, and
   - documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy.

   RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
Alpelisib	PIQRAY
apalutamide	ERLEADA
asparaginase (Erwinia chrysan)	ERWINAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
belinostat	BELEODAQ
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	BENDEKA
bendamustine HCl	TREANDA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
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
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
Daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
Darolutamide	NUBEQA
degarelix acetate	FIRMAGON
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
Enfortumab vedotin-ejfv	PADCEV
Entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idelalisib	ZYDELIG
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI

lenvatinib mesylate	LENVIMA
lorlatinib	LORBRENA
Lurbinectedin	ZEPZELCA
Lutetium Lu 177 dotate	LUTATHERA
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
Pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
Pexidartinib	TURALIO
Polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib HCl	ICLUSIG
pralatrexate	FOLOTYN
ramucirumab	CYRAMZA
regorafenib	STIVARGA
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
Ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
Sacitizumab govitecan-hziy	TRODELVY
Selinexor	XPOVIO
Selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE

sonidegib phosphate	ODOMZO
Tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
Tazemetostat	TAZVERIK
tisagenlecleucel	KYMRIAH
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-pkrb	HERZUMA
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-qyyp	TRAZIMERA
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trifluridine/tipiracil HCl	LONSURF
Tucatinib	TUKYSA
vandetanib	CAPRELSA
vandetanib	VANDETANIB
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

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

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Orphan Drug Policy: Prior Authorization Update

Purpose of the Update:
This update modifies the orphan drug policy based on an expanded indication for bruosumab-twza (**Table 1**). 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.

Table 1. Expanded indications for drugs under the Orphan Drug Policy

Generic Name (Brand)	Expanded Indication	Year of Approval	FFS Utilization Since Initial Approval (2018)	Relevant ICD-10 codes	FFS patients with claims for relevant ICD-10 codes*
Burosumab-twza (Crysvita®)	FGF23-related hypophosphatemia in tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older	2020	0	M83.8 Other adult osteomalacia M83.9 Adult osteomalacia, unspecified	M83.8: 2 M83.9: 13

* Estimated based on number of patients with FFS medical claims with the indicated diagnosis over a 1 year period (1/01/2019 to 12/31/2019). Diagnoses are based on ICD-10 codes associated with medical claims data, may not exactly match the FDA-approved indication, and may not reflect members *currently* enrolled in FFS.

Recommendation:

- Modify PA to support medically appropriate use of burosumab-twza based on expanded FDA indication.

Appendix 1. Prescribing Information Highlights

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

CRYSVITA® (burosumab-twza) injection, for subcutaneous use
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	6/2020
Dosage and Administration, Tumor-induced Osteomalacia (2.4)	6/2020
Dosage and Administration, 25-Hydroxy Vitamin D Supplementation (2.7)	9/2019

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

CRYSIVTA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for:

- The treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older. (1.1)
- The treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older. (1.2)

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

For subcutaneous use only (2)

- Pediatric XLH (6 months and older):
  - For patients who weigh less than 10 kg, starting dose regimen is 1 mg/kg of body weight rounded to the nearest 1 mg, administered every two weeks (2.2)
  - For patients who weigh 10 kg and greater, starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.2)

  Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus. (2.2)
- Adult XLH: Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four weeks. (2.3)
- Pediatric TIO (2 years and older): Starting dose is 0.4 mg/kg of body weight rounded to the nearest 10 mg every 2 weeks. Dose may be increased up to 2 mg/kg not to exceed 180 mg, administered every two weeks. (2.4)
- Adult TIO: Starting dose is 0.5 mg/kg every four weeks. Dose may be increased up to 2 mg/kg not to exceed 180 mg, administered every two weeks.(2.5)

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

Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL in a single-dose vial (3)

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

- With oral phosphate and/or active vitamin D analogs. (4)
- When serum phosphorus is within or above the normal range for age. (4)
- In patients with severe renal impairment or end stage renal disease. (4)

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

- Hypersensitivity: Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment. (5.1)
- Hyperphosphatemia and Risk of Nephrocalcinosis: For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels. (5.2, 6.1)
- Injection Site Reactions: Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment. (5.3, 6.1)

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

- Most common adverse reactions (≥25% in the CRYSVITA group and > Active Control) in pediatric XLH patients are: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries. (6.1)
- Most common adverse reactions (>5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless legs syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, blood phosphorus increased. (6.1)
- Most common adverse reactions (>10%) in TIO patients are: tooth abscess, muscle spasms, dizziness, constipation, injection site reaction, rash, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2020

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
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 months TIO ≥ 2 years	Pediatric <18 years: Initial (administered SC ~~subcutaneously~~ every 2 weeks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg)	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (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)

			TIO: 0.5 mg/kg monthly initially (Max 2 mg/kg or 180mg every 2 weeks)	
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 years	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Luspatercept (REBLOZYL)	Anemia (Hg <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hg <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 years	Initial: 1 mg/kg subcutaneously Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia Max dose of 1.75 mg/kg every 3 weeks for myelodysplastic syndromes	Baseline Monitoring/Documentation • Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 weeks in patients with myelodysplastic syndromes • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 weeks) • Hemoglobin level • Blood pressure

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

Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** Approve for up to 3 months (or length of treatment) whichever is less Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
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
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: 8/20; 6/20 (SS); 2/20
Implementation: 7/1/20

ProDUR Report for April through June 2020
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	7	2	0	5	0.01%	28.6%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,554	387	0	1,166	1.30%	24.9%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	178	44	0	134	0.12%	24.7%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	79,742	15,474	39	64,226	68.37%	19.4%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	24,901	6,590	3	18,289	21.37%	26.5%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	733	119	0	614	0.60%	16.2%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	3	1	0	2	0.01%	33.3%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	835	254	0	581	0.67%	30.4%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	520	145	0	375	0.40%	27.9%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	23	17	0	6	0.02%	73.9%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,977	2,242	0	5,731	6.80%	28.1%
		Totals	**116,473**	**25,275**	**42**	**91,129**	**99.66%**	**21.7%**

ProDUR Report for April through June 2020
Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,451	228	1,223	12,739	11.4%	15.7%
ER	Lorazepam	458	125	333	11,656	3.9%	27.3%
ER	Alprazolam	212	44	168	7,821	2.7%	20.8%
ER	Diazepam	128	23	105	4,182	3.1%	18.0%
ER	Buspirone (Buspar)	1,771	484	2,287	27,281	6.5%	27.3%
ER	Lamictal (Lamotrigine)	4,885	939	3,946	39,389	12.4%	19.2%
ER	Seroquel (Quetiapine)	3,977	862	3,115	27,751	14.3%	21.7%
ER	Zyprexa (Olanzapine)	2,331	527	1,804	17,599	13.2%	22.6%
ER	Risperdal (Risperidone)	1,927	408	1,519	13,546	14.2%	21.2%
ER	Abilify (Aripiprazole)	3,106	579	2,527	23,696	13.1%	18.6%
ER	Wellbutrin (Bupropion)	5,137	886	4,251	53,423	9.6%	17.2%
ER	Hydrocodone/APAP	14	2	12	1,143	1.2%	14.3%
ER	Oxycodone	18	7	11	1,295	1.4%	38.9%
ER	Tramadol	10	4	6	403	2.5%	40.0%
ER	Suboxone (Buprenorphine/Naloxone)	115	44	71	2,221	5.2%	38.3%
ER	Zoloft (Sertraline)	6,206	1,140	5,066	65,432	9.5%	18.4%
ER	Prozac (Fluoxetine)	4,165	747	3,418	44,632	9.3%	17.9%
ER	Lexapro (Escitalopram)	3,471	641	2,828	37,992	9.1%	18.5%
ER	Celexa (Citalopram)	2,125	303	1,822	25,220	8.4%	14.3%
ER	Trazodone	5,940	1,084	4,856	53,923	11.0%	18.2%
ER	Cymbalta (Duloxetine)	3,906	672	3,234	40,158	9.7%	17.2%
ER	Intuniv (Guanfacine)	1,690	206	1,484	11,955	14.1%	12.2%

ProDUR Report for April through June 2020
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	4,758	78	256	1,002	5	2,453	778	1	185
ER	February	3,378	64	218	739	4	1,896	324	0	133
ER	March	3,470	128	253	756	2	1,932	276	0	123
	Total =	**11,606**	**270**	**727**	**2,497**	**11**	**6,281**	**1,378**	**1**	**441**
	Percentage of total overrides =		**2.3%**	**6.3%**	**21.5%**	**0.1%**	**54.1%**	**11.9%**	**0.0%**	**3.8%**

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	953	367		
		Unique Patients Identified	1202	384		
		Total Faxes Successfully Sent	697	280		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	415	140		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$40,730	$8,024		
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	341	96		239
		Unique Patients Identified	371	97		254
		Total Faxes Successfully Sent	256	76		170
		Prescriptions Changed to Recommended Within 6 Months of Intervention	159	57		57
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$155,736	$37,004		$9,578

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	64	51	79	25
		Total Faxes Successfully Sent	40	25	45	9
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	14	7	16	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	12	5	6	
		Prescriptions Unchanged after 3 Months of Fax Sent	34	27		
		Safety Monitoring Profiles Identified	4	6	4	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$73,613	$53,126	$31,507	

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified	990	675	1046	344
		Profiles sent for expert review	10	5	11	2
		Prescribers successfully notified	8	5	7	
		Patients with change in antipsychotic drug in following 90 days			2	
		Patients with continued antipsychotic therapy in the following 90 days	9	5	9	
		Patients with discontinuation of antipsychotic therapy in the following 90 days	3		1	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	67	56	65	20
		Total prescribers identified	66	56	63	20
		Prescribers successfully notified	57	56	61	14
		Patients with claims for the same antipsychotic within the next 90 days	33	22	35	5
		Patients with claims for a different antipsychotic within the next 90 days	5	3	2	1

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	71	71	139	31
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	17	6	19	4
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	134	110	199	35
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	9	8	13	5
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed		17	18	1
		RetroDUR_Letters Sent To Providers		5	7	1
		Provider Responses		0	0	0
		Provider Agreed / Found Info Useful		0	0	0
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	10	5		
		RetroDUR_Letters Sent To Providers	1			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
	Lock-In	RetroDUR_Profiles Reviewed	11	24	17	11
		RetroDUR_Letters Sent To Providers		2		
		Provider Responses		0		
		Provider Agreed / Found Info Useful		0		
		Locked In	0	2	0	0
	Polypharmacy	RetroDUR_Profiles Reviewed	29	36	2	20
		RetroDUR_Letters Sent To Providers	8	3		7
		Provider Responses	0	1		0
		Provider Agreed / Found Info Useful	0	1		0

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Combination Opioid-Sedative	Total patients identified	93	98	136	29
		Total prescribers identified	93	97	135	29
		Prescribers successfully notified	78	97	132	21
		Patients with discontinuation of therapy within next 90 days	15	13	25	23
		Patients with new prescription for naloxone within next 90 days	2	2	3	1
		Average number of sedative drugs dispensed within next 90 days	0	0	0	0
		Average number of sedative prescribers writing prescriptions in next 90 days	0	0	0	0
	ICS/LABA	Disqualified	2	4	5	
		Disqualified - Erroneous denial	2	4	5	
		Faxes Sent	2	1		
		Fax Sent - Combination Inhaler	2	1		
	TCAs in Children	Total patients identified		5	11	2
		Total prescribers identified		5	11	2
		Prescribers successfully notified		3	8	
		Patients with claims for a TCA within the next 90 days		1	4	
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days			1	

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AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
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Biosimilar Medications: Key Considerations for Providers

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Introduction

Biologic therapies are large proteins that are developed using recombinant DNA technology in living systems and extracted via complex purification techniques.[1] Biologics include hormones, cytokines, clotting factors, and monoclonal antibodies. They are used to treat diabetes, hemophilia, cancer and autoimmune conditions. Although the overall number of prescriptions for biologics is relatively modest compared with that for small-molecule medications, their development and production are associated with significant costs.[1] Administration of a biologic agent to an individual patient ranges between $15,000 and $150,000 per year.[1] Biologics are also among the most expensive drugs, accounting for about 40% of total United States (US) pharmaceutical expenditures despite being used by less than 2% of Americans.[2] Medications that have similar properties to Food and Drug Administration (FDA)-approved biologics are termed biosimilars.[1] There are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity and potency of the product.[3] Biosimilars were introduced into the European markets in 2005 in an effort to improve patient access to life-saving medications. This newsletter will review current trends and regulations in the biosimilar United States (US) market.

FDA Guidance for Biosimilar Approval

The Biologics Price Competition and Innovation (BPCI) Act of 2009 was included as part of the Affordable Care Act (ACA) health-care-reform legislation enacted in 2010.[4] The BPCI Act created an abbreviated licensure pathway for biological products shown to be biosimilar with an FDA-licensed reference product. This regulation allowed the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing its product was "highly similar" to an approved product.[4] The FDA guidance describes the process required to demonstrate biosimilarity, beginning with comprehensive structural and functional analyses, followed by animal studies to assess toxicity, and clinical studies on pharmacokinetics, pharmacodynamics, and immunogenicity.[1] A summary of currently approved biosimilars is presented in **Table 1.** Seven FDA-approved biosimilars have not yet been marketed due to patent litigation. More approvals are expected in the next few years because a patent cliff for biologics is imminent in the United States, with an estimated $100 billion worth of biologics set to lose patent exclusivity in 2020.[5]

Table 1. FDA-Approved Biosimilars

Reference Product	Biosimilar Products
AVASTIN (bevacizumab)	ZIRABEV (bevacizumab-bvzr) MVASI (bevacizumab-awwb)
ENBREL (etanercept)	ERELZI (etanercept-szzs)* ETICOVO (etanercept-ykro)*
EPOGEN (epoetin-alfa)	RETACRIT (epoetin-alfa-epbx)
HERCEPTIN (trastuzumab)	KANJINTI (trastuzumab-anns) TRAZIMERA (trastuzumab-qyyp) ONTRUZANT (trastuzumab-dttb) HERZUMA (trastuzumab-pkrb) OGIVRI (trastuzumab-dkst)
HUMIRA (adalimumab)	ABRILADA (adalimumab-afzb)* HADLIMA (adalimumab-bwwd)* HYRIMOZ (adalimumab-adaz)* CYLTEZO (adalimumab-adbm)* AMJEVITA (adalimumab-atto)*
NELUASTA (pegfilgrastim)	ZIEXTENZO (pegfilgrastim-bmez) FULPHILA (pegfilgrastim-jmdb) UDENYCA (pegfilgrastim-cbqv)
NEUPOGEN (filgrastim)	NIVESTYM (filgrastim-aafi) ZARXIO (filgrastim-sndz)
REMICADE (infliximab)	AVSOLA (infliximab-axxq) IXIFI (infliximab-qbtx) RENFLEXIS (infliximab-abda) INFLECTRA (Infliximab-dyyb)
RITUXAN (rituximab)	RUXIENCE (rituximab-pvvr) TRUXIMA (rituximab-abbs)

*Not yet Available In The United States Due To Patent Litigation

Biosimilar Interchangeability

A provision of the BPCI Act created a second level of approval that goes beyond biosimilarity, called interchangeability.[6] An interchangeable biological product is a product that has been shown to be biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient.[3] The FDA considers the totality of the evidence when evaluating proposed interchangeable products and recommends a stepwise approach for generating data to support a demonstration of interchangeability.[7] The Purple Book provides a listing of all originator, biosimilar, and interchangeable biosimilar products approved by the FDA.[8] As of March 2020, no biosimilar products have received the interchangeability designation from the FDA.

Interchangeable designation may permit substitution of biosimilars for the originator without intervention of the prescriber; however, US substitution policies are determined

by state laws, not by the FDA. State legislation varies, but typically requires FDA approval of a product as interchangeable. Interchangeability of biosimilars differs from generic substitution, whereby a reference drug is substituted by a generic version of the drug that is identical with respect to active ingredients and strength, concentration, dosage form, and route of administration.[9] In most states, pharmacists must notify prescribers and patients and retain records of interchangeable biosimilar substitutions.

In Oregon, biosimilar legislation is addressed in OAR 855-041-1105.[10] The biosimilar rule states: A pharmacy or pharmacist filling a prescription or order for a biological product may not substitute a biosimilar product for the prescribed biological product unless:
(a) The biosimilar product has been determined by the FDA to be interchangeable with the prescribed biological product;
(b) The prescribing practitioner has not designated on the prescription that substitution is prohibited;
(c) The patient for whom the biological product is prescribed is informed of the substitution prior to dispensing the biosimilar product;
(d) The pharmacy or pharmacist provides written, electronic or telephonic notification of the substitution to the prescribing practitioner or the prescribing practitioner's staff within three (3) business days of dispensing the biosimilar product; and
(e) The pharmacy or pharmacist retains a record of the substitution for a period of not less than three (3) years.[10]

Extrapolation of Approved Indications

Biosimilars are not required to have clinical data in each indication for which licensure is sought. Regulatory guidelines permit extrapolation of clinical data from one indication to support biosimilar approval for use in an indication that was not directly compared to the biologic in a clinical trial but for which the reference product is approved.[8] Extrapolation must be scientifically justified and based on the totality of the evidence from all stages of biosimilar development.[7] For example, Celltrion secured the FDA approval of its biosimilar infliximab for all indications of the original infliximab (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis) by conducting comparative clinical studies in just rheumatoid arthritis and ankylosing spondylitis.[7]

Insulin Biosimilar Projections in the US

In the US, insulins are considered biological products but were historically approved through traditional FDA pathways under section 505 of the Food Drug and Cosmetic (FD&C) Act as a "follow on medication". Growth and reproductive hormones have also been approved as follow on medications and are not designated as generics. The BCPI Act stipulates that effective March 2020, an approved application for a biological product under the FD&C Act will be deemed to be a license for the biological product. Therefore, all newly developed products similar to a licensed biologic will be approved through the biosimilar pathway.

Incorporating Biosimilars into Practice

There are many challenges associated with introduction of new biosimilars, all of which could affect product uptake.[9] In some cases, multiple biosimilars are available; however, not all have the same indications as the reference product.[9] Additionally, differences in product presentation and the need for devices or auto-injectors, between a biosimilar and the reference product or among biosimilars could create confusion.[9] There are also challenges associated with reimbursement, patient preference, incorporation into electronic medical records (i.e. order sets), greater acceptance of biosimilars for supportive care versus more complex therapeutic indications, and limited pharmacy space.[9]

Conclusions

Biosimilars have the potential to increase accessibility to and expand the use of biologic therapies. Biosimilar approval is granted through FDA regulatory pathways that are distinct from small-molecule generics and novel therapeutics. Evolving regulatory guidelines for interchangeability may influence substitution practices and post-marketing pharmacovigilance, as well as the type and extent of information pharmacists can communicate to patients and other health care providers about biosimilar products.[7]

Oregon Health Plan Biosimilar PA Criteria

- For biologic PA criteria, all biosimilars are currently non-preferred products. Adalimumab and etanercept are preferred agents in this class.
- Oncology biosimilars are all preferred with no PA restrictions.
- Colony stimulating factor biosimilars are non-preferred.

Peer Reviewed By: Kevin Russell, RPh, MBA, BCACP, Outpatient Pharmacy Operations Manager, Samaritan Health Services

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Coronavirus Management: Evidence for Treatment and Drug Shortage Updates

Based on publications through 4/13/2020

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Introduction

The coronavirus (SARS-CoV-2) is a novel virus first identified in December 2019 that has dramatically influenced the lives of many throughout the world. This virus has been associated with an infection called COVID-19 which can cause severe pneumonia and death in some patients.[1] There is intense interest in possible treatments, which has led to a number of recent publications and clinical trials in process. The purpose of this newsletter is to clearly summarize the current theorized treatments and assess their level of evidence, discuss the implications of off-label treatment given the current level of evidence, as well as identify best sources of information from appropriate regulatory bodies for clinicians who are navigating frontline work in the face of this epidemic, throughout Oregon and the United States (US). As information is constantly changing, we have created a website that has links to most appropriate sources for government agencies, clinical recommendations, available trials, and evidence as it becomes available: https://pharmacy.oregonstate.edu/drug-policy/newsletters/coronavirus-management.

Drug Therapy

A plethora of medications with anti-inflammatory, immunomodulatory and/or antiviral properties are being studied for the treatment of COVID-19 (Table 1). At this point, no medications have high-quality data supporting their use.[1-4] The following is a short synopsis of the available published data, potential side effects and current place in therapy for medications being used for COVID-19.

Table 1: Investigational drugs and recommendations

Drug	Recommendation from current data	Doses (if applicable)
Hydroxychloroquine sulfate (HCQ) or Chloroquine (CQ)	• Benefit uncertain for inpatient use.[5,6] • No evidence for outpatient use or prophylaxis • Prioritize use for FDA labeled indications (e.g., lupus) given shortages.	HCQ 800 mg Day 1 then 400 mg x 3-7 days[7] CQ 1000 mg first day then 500 mg x 3-7 days[8]
Concomitant Azithromycin with HCQ	• Benefit uncertain for inpatient use. • No evidence for outpatient use or prophylaxis	500 mg day 1, 250 mg Day 2-5[5]
Lopinavir/Ritonavir	• Efficacy not established, use not recommended at this time outside of clinical studies[9]	
Remdesivir	• Insufficient evidence • Promising in vitro activity • Enroll patients in clinical trials when possible.[10-12]	
Corticosteroids	• Use not recommended unless other indication[10]	
NSAIDs	• No change for chronic medications • Can consider acetaminophen[10]	
ACEI and ARB	• No change in therapy recommended[10,13]	

Hydroxychloroquine/Chloroquine ± Azithromycin

Chloroquine and hydroxychloroquine (HCQ) have been hypothesized to have immunomodulating effects and cause a disruption of PH dependent steps of viral replication, such as fusion and uncoating.[14] Some studies have included azithromycin due to its anti-inflammatory and immunomodulatory activity. Overall, there is a lack of high-quality data on the use of these agents in COVID-19.

A randomized, controlled trial of HCQ 200 mg twice daily for 5 days versus standard care in 62 patients was just published, though not peer-reviewed.[6] The study was blinded with equal numbers in both groups, though it is unclear if there was a placebo to maintain blinding. Patients were admitted to the hospital with mild COVID-19 pneumonia. The mean age was 44.7 years (standard deviation 15.3 years), and comorbidities were not reported. Four patients progressed to severe illness, all in the standard care group. Pneumonia, based on change in CAT scan from day 0 to day 6, appears improved, though the outcome of percentage of pneumonia absorption at day 6 is a non-traditional endpoint.

Additionally, a study from China of HCQ is available, though only the abstract is published in English.[15] This study included 30 patients randomized to HCQ 400 mg daily for 5 days or placebo; the presence of blinding is unclear. Endpoints included oropharyngeal viral clearance at day 7, median duration of hospitalization, median time to body temperature normalization, radiological progression, and adverse events. There were no statistically significant differences in any endpoint between the groups.

A published letter[16] describes that over 100 patients enrolled in 15 studies have shown superiority of chloroquine over control

treatment for the outcomes of inhibiting exacerbation of pneumonia, improving radiological findings, viral clearance, and reduction of disease course. The details of these trial designs and data of the results are not yet published. A February 15th, 2020 conference in China used these results to add chloroquine to the People's Republic of China guidelines for the treatment of COVID-19.

A non-randomized, open-label study[5] from France has been criticized by the medical community for publication due to the very low quality of the research methodology and inability to draw valid conclusions from the results. It evaluated HCQ 200 mg three times day for 10 days in 14 patients and HCQ (same dose) + azithromycin 500 mg on day 1, then 250 mg daily for next 4 days in 6 patients. These 20 patients were compared to 16 control patients, many of which were being treated at other hospitals. An additional 6 patients (6 of 26) receiving HCQ were lost to follow up and were not included in the per protocol analysis. The endpoint was nasopharyngeal viral clearance at day 6. While there was a statistically significant reduction in clearance by day 6 in those receiving HCQ compared to control (70% vs. 12.5%; p=0.001), and this difference was more pronounced when looking only at patients in the HCQ + azithromycin arm compared to HCQ alone (100% vs 57.1%), there are many important drawbacks. This small study was open-label, non-randomized, and had a high rate of attrition. There was no standardization related to the severity of the COVID-19 infection, nor results of clinical indicators related to the treatment. There were significant differences between the HCQ and HCQ + azithromycin group, but the group sizes were extremely small and it is unclear if azithromycin adds any clinical benefit. The extension of this study using the combination did not include a control group to allow comparison.[17] The significant attrition also introduces attrition bias, and of those 6 patient withdrawals, 3 went to the intensive care unit, 1 died, 1 discharged from the hospital on day 3, and 1 had intolerable nausea and vomiting.

HCQ has important side effects, including bone marrow suppression, cardiac and hepatic toxicity, as well as the theoretical risk of hemolytic anemia in patients with G6PD deficiency. The combination with azithromycin further increases the risk of QT prolongation. Patients in this study receiving both drugs were inpatients on daily electrocardiogram (ECG) monitoring and resulting QT measurements were not reported, therefore safety of this combination for outpatient use, particularly in those such as the elderly and those with underlying cardiovascular disease, is unknown. An 80 patient follow-up study of the combination did not report if there was any QTc prolongation when ECG monitoring was performed at baseline and every 2 days.[17]

At this point, the use of HCQ and chloroquine in select inpatients may be reasonable as it may reduce time to viral clearance. Utility of the addition of azithromycin is unclear and requires additional monitoring. Overall quality of data is very low and additional studies are needed to determine if viral clearance reduces disease severity, morbidity, and mortality. Use in outpatients is not yet supported by evidence, and widespread use is not appropriate given risk of shortages of these medications for patients with autoimmune disorders.

Lopinavir/Ritonavir

After case reports and *in vitro* data suggesting that the HIV protease inhibitors lopinavir/ritonavir have activity against Middle Eastern Respiratory Syndrome (MERS-CoV), researchers in China conducted a randomized, open-label trial with lopinavir 400 mg/ritonavir 100 mg orally twice daily versus standard care for 14 days in hospitalized adults with COVID-19, pneumonia on chest imaging, and impaired oxygenation.[9] Patients were stratified by level of oxygen support at enrollment and followed for 28 days or until hospital discharge or death and analyzed using an intention-to-treat method. The primary endpoint was time to clinical improvement defined as a 2-point improvement on a 7-point ordinal scale. Multiple other clinical, virologic, and safety endpoints were included such as: duration of hospitalization, viral detection over time, and adverse events during treatment. Enrollment was suspended when another investigational agent became available for study. There was no statistical difference in the primary endpoint of time to clinical improvement. The intervention group showed a 15.5% between group difference (45.5% vs 30%; confidence interval 2.2 to 28.8) in the secondary outcome of clinical improvement at day 14, but other clinical, virologic, and safety comparisons were not significant. Notably, 14% of lopinavir/ritonavir patients were unable to complete 14 days of therapy secondary to gastrointestinal side effects, 2 had serious acute gastritis, and 2 developed self-limiting skin eruptions. There were also several protocol violations related to receipt or non-receipt of investigational treatment by randomized group and roughly 1/3 of patients in both groups received glucocorticoids. Use of this combination outside of clinical trials is not yet warranted.

Remdesivir

Remdesivir is an investigational antiviral with significant potential for use in COVID-19 infections based on *in vitro* data of inhibition of an RNA dependent RNA polymerase and experimental use in Ebola and MERS-CoV infections.[18] There are multiple clinical trials underway for use in COVID-19 infections.[3,11] The manufacturer was allowing use of this medication outside of the clinical trial setting with a compassionate use protocol. However, due to immense demand, availability has been suspended while transitioning to an expanded access program. Exceptions will only be

considered for those with severe disease who are pregnant or under 18 years.[10,12] Preliminary results of single arm, open-label use of remdesivir via compassionate use protocols were recently published.[19] The patients were required to be inpatients requiring oxygen support or saturating less than 94% on room air, with creatinine clearance of more than 30 ml/min, and without severe liver enzyme derangement. After 8 were excluded for missing information and an erroneous drug start date, the 53 remaining patients had a mortality rate of 13%. Those on invasive ventilation had a mortality rate of 18% after completion of study drug over the 10-day infusion protocol. Clinicians should give strong consideration to trial enrollment for COVID-19 patients in areas where these trials are offered.

Medications to avoid: True or False?

Corticosteroids, NSAIDs, ACEI, and ARBs

There are reports that some medications should be avoided in patients with suspected COVID-19. Corticosteroids are currently not recommended for routine use to treat COVID-19 patients unless there are other indications.[10] Conflicting data indicate that there may be benefit in very severe cases, but these data come with many biases and limitations.[3,10] Methylprednisolone and dexamethasone are currently being studied in a least one trial each.[10,11] More information should be available once these have concluded.

Use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have both also come into question due to COVID-19. The binding mechanism of the virus utilizes angiotensin-converting enzyme (ACE) type 2. This has led to speculation of both harm and benefit.[10] Losartan is being studied as a therapy for COVID-19. Until more data are available, no change in therapy is currently recommended for agents that affect the renin-angiotensin aldosterone system, and this recommendation is supported by professional cardiology societies.[13]

News reports have stated that non-steroidal anti-inflammatory medications (NSAID), such as ibuprofen, can worsen COVID-19 outcomes. This is due to an unsubstantiated link to increases of ACE type 2 expression in NSAID users.[10] At this time, the data behind these assertions are anecdotal. The FDA currently makes no recommendations to avoid use, though for those without contraindications, acetaminophen can be used for management of pain or fever as an alternative.[2,10] Patients taking NSAIDs or aspirin for chronic conditions should continue unless other clinical reasons necessitate a change.

Ongoing studies and data

There are a number of trials throughout the world and the US evaluating therapies for treatment and prophylaxis of COVID-19, including several in the Portland area.[10,11] Please see our website or clinicaltrials.gov for current updates on available clinical trials in Oregon.

Many additional agents have been purported to have potential use in COVID-19 infection by direct antiviral effect or reduction of inflammatory immune response. Tocilizumab in particular has garnered much interest for patients with high interleukin-6 levels and cytokine release, often seen in severe COVID-19 pneumonia.[10] However, data remain limited as a randomized controlled trial in China is underway and a manufacturer sponsored global trial is being implemented.[10] Agents below are being researched but currently have minimal human data to recommend use outside of a formal clinical trial setting: arbidol, ascorbic acid, aviptadil, bevacizumab, bromhexine, carrimycin, cobicistat, darunavir, eculizumab, favipiravir, fingolimod, interferon, oseltamivir, pirfenidone, ribavirin, sarilumab, tetrandrine, thalidomide, and various traditional Chinese medicines.[10,11]

Shortages

The development of this pandemic has resulted in widespread shortages of hospital supplies, including drug products. Shortages have been reported for HCQ, which is an essential medication for patients with lupus and other chronic diseases. To avoid further shortages, all prescriptions written for the off-label treatment of COVID-19 should be reviewed for appropriateness and patients should be educated to avoid hording and stockpiling of medications. Patients should be encouraged to keep an adequate supply of at least two weeks on hand of chronic medications and advised that pharmacies will remain open during this time. Additionally, many local pharmacies are offering mail or delivery services to avoid interactions during this public health emergency. Early refills and conversion of prescriptions from 1 month to 3 month fills can result in worsening of shortages. Additionally, shortages of products manufactured in places like China may be delayed, though the specific products are not known. Continue to monitor the ASHP or FDA website for information and alternatives as these occur.[10]

Regulatory Guidance for Oregon

On March 25th, 2020, the Oregon Board of Pharmacy instituted a temporary administrative order during the COVID-19 public health emergency (855-007-0085) to restrict use of hydroxychloroquine and chloroquine to chronic therapy for approved indications and proven COVID-19 infections in hospitalized patients.[20]

This order came 2 days after the Oregon Boards of Pharmacy and Medicine issued a joint statement of disapproval for false or inappropriate prescribing in a time of crisis.[21] The reasons prompting the writing of this statement were[21]:

- Creating the risk of adverse effects and additional harm.
- Creating shortages of therapies for patients who have legitimate medical need for the drug's intended purpose and use.
- Confounding the interpretation of efficacy (particularly when randomized controlled studies are necessary and are currently underway).
- Providing false hope to patients or a false sense of security.

The FDA has issued Emergency Use Authorizations for both medications for certain inpatients as well.[4]

Conclusions

Providers are encouraged to consult recommended sources for the current recommendation on the most appropriate way to manage COVID-19. At this time there are no data to recommend a therapy for prophylaxis, and outpatient therapy should focus on supportive care and reducing risk of transmission. Additionally, based on the overall uncertainty of risks and benefits, it is best to administer all treatments in the context of a clinical trial if possible.[22] Best practices and appropriate prescribing should be adhered to now more than ever to maintain quality patient care and preserve needed resources for those conditions in which there is evidence for use.

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OHSU Drug Effectiveness Review Project Summary Report: Newer Diabetes Drugs and Cardiovascular Disease Outcomes

Date of Review: August 2020

Date of Last Review: GLP-1 Receptor Agonists (March 2019)
DPP-4 inhibitors (July 2018)
SGLT-2 inhibitors (July 2018)
Literature Search: 1/01/2018 - 4/09/2020

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

Research Questions:
1. In adults with type 2 diabetes mellitus (T2DM), what is the evidence for cardiovascular (CV) benefit for newer diabetes drugs, including mortality?
2. In adults with T2DM, what harms are associated with newer diabetes drugs that have led to treatment discontinuation or determined to be a severe adverse event that has been prespecified as a severe adverse event of interest (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection)?
3. Does the effectiveness differ in patients with or without prior cardiovascular disease (CVD)?

Conclusions:
- A 2020 Drug Effectiveness Review Project (DERP) report and one randomized controlled trial provided evidence for the review.
- The DERP report serves as the main evidence for this review. All studies in the report included patients with T2DM and a majority of patients were at high risk for CV disease or established CV disease.
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (exenatide extended release (ER), liraglutide and sematglutide) demonstrated a small risk reduction in all-cause mortality (absolute risk reduction [ARR] of 1.0% to 1.4% and number needed to treat [NNT] of 71-100) in patients with T2DM based on moderate evidence (median study durations from 2.1 to 3.8 years).[1] There was a neutral effect on risk of hospitalizations for heart failure (HF) in comparisons between GLP-1 RAs and placebo based on moderate quality of evidence.
- Dipeptidyl peptidase-4 (DPP-4) inhibitors were reported as having a neutral effect on all CV outcomes (all-cause mortality, stroke, myocardial infarction [MI], hospitalization for heart failure) based on low to moderate quality of evidence.[1] There was an increased risk of hospitalizations for HF based on low quality of evidence from one saxagliptin trial (ARR 0.7%; number needed to treat [NNT] 143).
- Sodium-glucose transport protein 2 (SGLT-2) inhibitors significantly reduced the risk of hospitalization due to HF.[1]
    - Canagliflozin, dapagliflozin, empagliflozin were reported to have a reduced risk of hospitalizations due to heart failure (NNT 42-80) in studies lasting 2.6 to 3.1 years based on moderate quality of evidence.[1]
    - Empagliflozin reduced all-cause mortality compared to placebo, 5.7% vs. 8.3% (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001; ARR 2.6%/NNT 38 over a median follow up of 3.1 years).[1]

- Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).[1]
- In patients, with and without T2DM (41% with diabetes), and a history of HF and reduced injection fraction, dapagliflozin reduced the composite outcome of worsening heart failure or CV death, 16.3% vs. 21.2% (HR 0.74; 95% CI, 0.65 to 0.85; P<0.001; ARR 4.9%/NNT 20 over a median of 18.2 months).[2]

Recommendations:
- Recommend that newer diabetic therapies (DPP-4 inhibitors, GLP-1 RAs and SGLT-2 inhibitors) be second-line treatment options. Remove requirement for step therapy other than metformin.
- Recommend removing step therapy requiring sulfonylurea trial in prior authorization (PA) criteria for DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors.
- Evaluate comparative drug costs in executive session.

Summary of Prior Reviews and Current Policy
- Review of the evidence for GLP-1 receptor agonists in March of 2019 resulted in changes in the PA criteria to allow use of basal insulin with GLP-1 receptor agonists and auto-PA preferred products for patients with claims for metformin use in the previous 40 days. After executive session exenatide vials (Bydureon®) and liraglutide (Victoza® 2 and 3 Pak) were added to the Practitioner-Managed Prescription Drug Plan (PMPDP).
- No changes were made after presentation of newer diabetes medications. The requirement of trial of amylin analogs was removed from the SGLT-2 criteria. Semaglutide injection and ertugliflozin were maintained as non-preferred on the PMPDP.
- Evidence supporting current Oregon Health Administration (OHA) Fee-for-Service (FFS) policy came from the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) which recommends metformin as first-line therapy and consideration of sulfonylureas as an option for second-line therapy.
- Prior review of CV outcomes for newer diabetes drugs have demonstrated a neutral or small benefit over placebo with a major limitation of evidence is studies only in patients with CV disease or at high risk for CV disease.
- Current Oregon Health Plan (OHP) fee-for-service policy for newer diabetes treatment allows for the use of the GLP-1 RAs, Bydureon® and Victoza®, without prior authorization (PA) if prescribed in conjunction with, or record of prior use as described above, with metformin. DPP-4 inhibitors require a PA with a requirement of a trial of metformin and a sulfonylurea, or contraindications to these drugs, as outlined in the PA criteria in **Appendix 1**. The DPP-4 inhibitor, sitagliptin, is also a preferred drug but requires that patients meet specific clinical PA criteria. SGLT2 inhibitors are available as last-line therapy as described in the clinical PA criteria.
- Prescriber alignment with preferred agents is 41% for the GLP-1 RA class, 81% for the DPP-4 class and there are no preferred products designated in the SGLT-2 class.

Methods:
The 2020 drug class report on Newer Diabetes Drugs and Cardiovascular Disease Outcomes 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.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

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:
The focus of a recent review performed by the DERP was CV outcomes associated with newer diabetes drugs.[1] Adults with T2DM who received a SGLT-2 inhibitor, DPP-4 inhibitor or GLP-1 RA were included (**Table 1**). All patients were allowed standard of care for glucose control and CV risk management. Eligible studies included randomized clinical trials and prospective and retrospective cohort studies (≥10,000 patients) that were published from January 1, 2017 to October 2, 2019.[1] Sixteen randomized, controlled trials were identified, 15 of which were placebo-controlled and one active control that compared linagliptin to glimepiride.[1] Important outcomes studied were mortality (all-cause and CV), CV outcomes (fatal or nonfatal myocardial infarction [MI], fatal or nonfatal stroke, hospitalization for heart failure), serious adverse events and pre-specified adverse reactions (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection). Serious adverse events were investigator determined events related to study treatment causing permanent discontinuation and one of the adverse events of interest (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection).

Table 1. Newer Diabetes Drugs Eligible for Inclusion in DERP Cardiovascular Outcomes Report[1]

Class	Generic Names	Brand Names
SGLT-2 inhibitors	Ertugliflozin Empagliflozin Dapagliflozin Canagliflozin	Steglatro* Jardiance Farxiga Invokana
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
SGLT-2 inhibitor with DPP-4 inhibitor	Dapagliflozin-saxagliptin Empagliflozin-linagliptin	Qtern* Glyxambi*
SGLT-2 inhibitor with metformin	Ertugliflozin-metformin Empagliflozin-metformin ER Canagliflozin-metformin ER Empagliflozin-metformin Dapagliflozin-metformin ER Canagliflozin-metformin	Segluromet* Synjardy XR* Invokamet XR* Synjardy* Xigduo XR* Invokamet*
DPP-4 inhibitor with TZD	Alogliptin-pioglitazone	Oseni*
DPP-4 inhibitor with metformin	Linagliptin-metformin ER Alogliptin-metformin Sitagliptin-metformin ER Linagliptin-metformin	Jentadueto XR* Kazano* Janumet XR* Jentadueto*

	Saxagliptin-metformin ER Sitagliptin-metformin	Kombiglyze XR* Janumet*
GLP-1 agonists	Oral semaglutide Semaglutide Lixisenatide Dulaglutide Albiglutide Exenatide ER Liraglutide Exenatide	Rybelsus Ozempic Adlyxin Trulicity Tanzeum Bydureon Victoza Byetta
GLP-1 agonist with long-acting insulin	Liraglutide-insulin degludec U100/3.6 mg Lixisenatide-insulin glargine U100/33 mg	Xultophy* Soliqua*
Abbreviations: DPP-4 = dipeptidyl peptidase 4; ER = extended release; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; XR = extended release Key: * No studies met inclusion criteria		

The results for the effectiveness and harms data from the DERP report are divided by therapeutic class and presented in **Table 2**. The GLP-1 RAs were the only drug class that demonstrated a risk reduction in all-cause mortality, with about a 1% absolute difference between active treatment and placebo.[1] Moderate level of evidence found the risk of hospitalization for heart failure was not associated with risk or benefitl for the GLP-1 RA class compared to placebo. Lack of precision amongst the class weakens the conclusions of these results.

GLP-1 RA:

All-cause mortality:

- Exenatide extended release [ER] = 6.9% vs. placebo = 7.9% (hazard ratio [HR] 0.86; 95% CI, 0.77 to 0.97; P=0.02; ARR 1%/NNT 100 over a median of 3.2 years).[1]
- Liraglutide = 8.2% vs. placebo = 9.6% (HR 0.85; 95% CI, 0.74 to 0.97; P=0.02; 1.4%/NNT 71 over a median of 3.8 years).[1]
- Semaglutide = 1.4% vs. placebo = 2.8% (HR 0.49; 95% CI, 0.27 to 0.92; ARR 1.4%/ NNT 71 over a median of 2.1 years).[1]

Stroke:

- Dulaglutide = 3.2% vs. placebo = 4.1% (HR 0.76; 95% CI, 0.62 to 0.94; P=0.01; ARR 0.9%/NNT 90 over a median of 5.4 years).[1]

Myocardial infarction:

- Albiglutide 4.0% vs. placebo = 5.0% (HR 0.75; 95% CI, 0.61 to 0.90; P=0.003; ARR 1%/NNT 100 over a median of 1.6 years).[1]
- Liraglutide = 6.3% vs. placebo = 7.3% (HR 0.86; 95% CI, 0.73 to 1.00; P=0.05; ARR 1%/NNT 100 over a median of 3.8 years).[1]

Major Adverse Cardiovascular Events (MACE):

- Patients treated with liraglutide with single vascular disease at baseline demonstrated a risk reduction for MACE over patients without cardiovascular disease (CVD) at baseline (HR 0.82; 95% CI, 0.71 to 0.95); however, there was no effect in patients with polyvascular disease (HR 0.82; 95% CI, 0.66 to 1.02).[1]

- Risk of CV death was reduced with liraglutide in patients with single vascular disease at baseline compared to patients without single vascular disease (HR 0.67; 95% CI, 0.53 to 0.85); no effect was seen in patients with polyvascular disease.[1]
- Exenatide ER reduced all-cause mortality in patients without heart failure at baseline (HR 0.79; 95% CI, 0.69 to 0.92) but no reduction was seen in patients with preexisting heart failure.[1]
- Low quality evidence found a reduced risk of severe adverse reactions compared to placebo (driven by albiglutide, dulaglutide, semaglutide, and oral semaglutide.

DPP-4 Inhibitors:

Hospitalizations for Heart Failure:

- Saxagliptin increased risk of hospitalizations for heart failure compared to placebo (3.5% vs. 2.8%; HR 1.27, 95% CI, 1.07 to 1.51; P=0.007; ARR 0.7%/number needed to harm [NNH] 143 with a median follow up of 2.1 years).[1]

Severe Adverse Events:

- Saxagliptin = 41.4% vs. placebo = 39.6% (RR 1.05; 95% CI, 1.01 to 1.09; P=0.02; ARR 1.8%/NNH 56 with a median follow up of 2.1 years).[1]

MACE:

- No significant differences were found with any of the DPP-4 inhibitors.

SGLT-2 Inhibitors:

All-cause mortality:

- Empagliflozin = 5.7% vs. placebo = 8.3% (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001; ARR 2.6%/NNT 38 over a median follow up of 3.1 years).[1]

Hospitalizations for Heart Failure:

- Canagliflozin = 5.5/1000 patient-years vs. placebo 8.7/1000 patient-years (HR 0.67; 95% CI, 0.52 to 0.87 with a median follow up of 295 weeks)(CANVAS).[1]
- Canagliflozin = 4.0% vs. placebo = 6.4% (HR 0.61; 95% CI, 0.47 to 0.80; P<0.001; ARR 2.4%/NNT 42 over a median follow up of 2.62 years)(CREDENCE).[1]
- Dapagliflozin = 2.5% vs. placebo = 3.3% (HR 0.73; 95% CI, 0.61 to 0.88; ARR 0.8%/NNT 80 over a median follow up of 4.2 years).[1]
- Empagliflozin = 2.7% vs. placebo = 4.1% (HR 0.65; 95% CI, 0.50 to 0.85; P=0.002: ARR 1.4%/NNT 71 over a median follow up of 3.1 years).[1]

Severe Adverse Events:

- Canagliflozin = 33.5% vs. placebo = 36.7% (RR 0.91; 95% CI, 0.84 to 0.99; P=0.03).[1]
- Dapaliflozin = 34.1% vs. placebo 36.2% (RR 0.94; 95% CI, 0.91 to 0.98; P=0.005).[1]
- Empagliflozin = 38.2% vs. placebo 42.3% (RR 0.90; 95% CI, 0.85 to 0.96; P = 0.0007).[1]

MACE:

- Non-CV death was reduced in patients taking dapagliflozin who also had a history of heart failure (HR 0.50; 95% CI, 0.29 to 0.86; P=0.03).[1]
- Dapagliflozin reduced risk of CV death (HR 0.83; 95% CI, 0.73 to 0.95; P= 0.005; ARR 0.9%; NNT 111) and hospitalizations for heart failure (HR 0.73; 95% CI, 0.61 to 0.88; p-value not reported; ARR 0.8%; NNT 125) in patients with a history of heart failure and reduced ejection fraction.
- Dapagliflozin reduced MACE in patients with history of MI (HR 0.84; 95% CI, 0.72 to 0.99; P=0.04).
- Dapagliflozin reduced recurrent MI in patients with history of MI (HR 0.78; 95% CI, 0.63 to 0.95).[1]
- Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).[1]

There was insufficient evidence of efficacy and harms outcomes to compare monotherapy with combination therapy of newer diabetes drugs. This review was limited by the lack of head-to-head comparisons between drugs in different classes. Trials also may not have been long enough to sufficiently capture CV outcomes. Differences in standard of care may have also influenced the results. External validity may be reduced by the inclusion of patients with a 10 year or more history of diabetes with established CVD or at high risk of CVD. There is insufficient evidence on the CV implications of these therapies in patients who are not at high risk.

Table 2. Cardiovascular Outcomes for Newer Diabetes Medications Vs. Placebo[1]

Outcome	All-Cause Mortality	Stroke	Myocardial Infarction	Hospitalization for Heart Failure	Serious Adverse Events	Comments
Drug Class						
GLP-1 RA *7 trials*	*Small risk reduction* (moderate quality of evidence) Benefit: - Exenatide ER - Liraglutide - Semaglutide oral Neutral: - Albiglutide - Dulaglutide - Lixisenatide - Semaglutide inj	*No effect* (low quality of evidence) Benefit: - Dulaglutide Neutral: - Albiglutide - Exenatide ER - Liraglutide - Lixisenatide - Semaglutide oral No evidence: - Semaglutide inj	*No conclusion* (very low quality of evidence) Benefit: - Albiglutide - Liraglutide Neutral: - Dulaglutide - Exenatide ER - Lixisenatide - Semaglutide oral No evidence: - Semaglutide inj	*No effect* (moderate quality of evidence) Neutral: - Dulaglutide - Exenatide ER - Liraglutide - Lixisenatide - Semaglutide (oral and inj) No evidence: - Albiglutide	*Reduced risk* (low quality of evidence) Benefit: - Albiglutide - Dulaglutide - Semaglutide (oral and inj) No evidence: - Exenatide ER - Liraglutide - Lixisenatide	Only patients with an eGFR < 60 mL reported reductions in MACE with liraglutide (HR, 0.69; 95% CI, 0.57 to 0.85; P= 0.01)
DPP-4 Inhibitors *5 trials*	*No effect* *(moderate quality of evidence)* Neutral: - Alogliptin - Saxagliptin - Sitagliptin - Linagliptin	*No effect* *(moderate quality of evidence)* Neutral: - Saxagliptin - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(low quality of evidence)* Neutral: - Saxagliptin - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(low quality of evidence)* Harm: - saxagliptin Neutral: - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(moderate quality of evidence)* Harm: - Saxagliptin Neutral: - Alogliptin - Sitagliptin - Linagliptin	

SGLT-2 Inhibitors *4 trials*	*No effect (moderate quality of evidence)* Benefit: - Empagliflozin Neutral: - Canagliflozin - Dapagliflozin	*No effect (low quality of evidence)* Neutral: - Canagliflozin - Dapagliflozin - Empagliflozin	*No effect (moderate quality of evidence)* Neutral: - Canagliflozin - Dapagliflozin - Empagliflozin	*Significant risk reduction (moderate quality of evidence)* Benefit: - Canagliflozin - Dapagliflozin - Empagliflozin	*Significant risk reduction (moderate quality of evidence)* Benefit: - Dapagliflozin - Empagliflozin Neutral or benefit: (conflicting results) - Canagliflozin	Canagliflozin decreased risk of stroke in patients with an eGFR < 45 mL (HR 0.32; 95% CI, 0.11 to 0.96).
Abbreviations: DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; ER = extended release; GLP-1 = glucagon-like peptide 1; MACE = major adverse cardiovascular events; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; XR = extended release						

Randomized Controlled Trials:

A total of 134 citations were manually reviewed from the initial literature search. After further review, 133 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
McMurray, et al[2] Phase 3, PC, RCT	Dapagliflozin 10 mg daily Vs. Placebo (n=2373)	Patients with or without diabetes with NYHA class II, III, or IV HF and an ejection fraction of 40% or less	Composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death	Dapagliflozin: 386 (16.3%) Placebo: 502 (21.2%) HR 0.74 (95% CI, 0.65 to 0.85) P<0.001 ARR 4.9%/NNT 20 over a median of 18.2 months

Abbreviations: ARR – absolute risk reduction; CV – cardiovascular; HF – heart failure; HR – hazard ratio; NNT – number needed to treat; NYHA – New York Heart Association; PC – placebo-controlled; RCT – randomized controlled trial.

References

1. Drug Effectiveness Review Project. Newer Diabetes Drugs and Cardiovascular Disease Outcomes: Update. February 2020.

2. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303.

Appendix 1: Current Preferred Drug List

DPP-4 Inhibitors

Generic	Brand	Form	PDL
sitagliptin phos/metformin HCl	JANUMET	TABLET	Y
sitagliptin phosphate	JANUVIA	TABLET	Y
alogliptin benz/metformin HCl	ALOGLIPTIN-METFORMIN	TABLET	N
alogliptin benz/metformin HCl	KAZANO	TABLET	N
alogliptin benz/pioglitazone	ALOGLIPTIN-PIOGLITAZONE	TABLET	N
alogliptin benz/pioglitazone	OSENI	TABLET	N
alogliptin benzoate	ALOGLIPTIN	TABLET	N
alogliptin benzoate	NESINA	TABLET	N
linagliptin	TRADJENTA	TABLET	N
linagliptin/metformin HCl	JENTADUETO XR	TAB BP 24H	N
linagliptin/metformin HCl	JENTADUETO	TABLET	N
saxagliptin HCl	ONGLYZA	TABLET	N
saxagliptin HCl/metformin HCl	KOMBIGLYZE XR	TBMP 24HR	N
sitagliptin phos/metformin HCl	JANUMET XR	TBMP 24HR	N

GLP-1 receptor agonists

Generic	Brand	Form	PDL	Route
exenatide	BYETTA	PEN INJCTR	Y	SQ
exenatide microspheres	BYDUREON	VIAL	Y	SQ
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y	SQ
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y	SQ
albiglutide	TANZEUM	PEN INJCTR	N	SQ
dulaglutide	TRULICITY	PEN INJCTR	N	SQ
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N	SQ
exenatide microspheres	BYDUREON PEN	PEN INJCTR	N	SQ
lixisenatide	ADLYXIN	PEN INJCTR	N	SQ
semaglutide	OZEMPIC	PEN INJCTR	N	SQ
semaglutide	RYBELSUS	TABLET	N	PO

SGLT-2 inhibitors

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	N
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin propanediol	FARXIGA	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N

dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empagliflozin	JARDIANCE	TABLET	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Randomized Controlled Trial

A Trial to Evaluate the Effect of the Sodium-Glucose Co-Transporter 2 Inhibitor Dapagliflozin on Morbidity and Mortality in Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction (DAPA-HF)

John J V McMurray, David L DeMets, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, Anna M Langkilde, Felipe A Martinez, Olof Bengtsson, Piotr Ponikowski, Marc S Sabatine, Mikaela Sjöstrand, Scott D Solomon, DAPA-HF Committees and Investigators

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce the risk of incident heart failure hospitalization in individuals with type 2 diabetes who have, or are at high risk of, cardiovascular disease. Most patients in these trials did not have heart failure at baseline and the effect of SGLT2 inhibitors on outcomes in individuals with established heart failure (with or without diabetes) is unknown.

Design and methods: The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) is an international, multicentre, parallel group, randomized, double-blind, study in patients with chronic heart failure, evaluating the effect of dapagliflozin 10 mg, compared with placebo, given once daily, in addition to standard care, on the primary composite outcome of a worsening heart failure event (hospitalization or equivalent event, i.e. an urgent heart failure visit) or cardiovascular death. Patients with and without diabetes are eligible and must have a left ventricular ejection fraction ≤ 40%, a moderately elevated N-terminal pro B-type natriuretic peptide level, and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 . The trial is event-driven, with a target of 844 primary outcomes. Secondary outcomes include the composite of total heart failure hospitalizations (including repeat episodes), and cardiovascular death and patient-reported outcomes. A total of 4744 patients have been randomized.

Conclusions: DAPA-HF will determine the efficacy and safety of the SGLT2 inhibitor dapagliflozin, added to conventional therapy, in a broad spectrum of patients with heart failure and reduced ejection fraction.

Appendix 3: Search Criteria

Database(s): Ovid MEDLINE(R) ALL 1946 to April 08, 2020

Search Strategy:

#	Searches	Results

1	sitagliptin.mp. or Sitagliptin Phosphate/	2437
2	alogliptin.mp.	499
3	linagliptin.mp. or Linagliptin/	753
4	saxagliptin.mp.	729
5	sitagliptin.mp. or Sitagliptin Phosphate/	2437
6	exenatide.mp. or Exenatide/	3164
7	liraglutide.mp. or Liraglutide/	2811
8	albiglutide.mp.	194
9	dulaglutide.mp.	372
10	lixisenatide.mp.	441
11	semaglutide.mp.	356
12	canagliflozin.mp. or Canagliflozin/	1106
13	dapagliflozin.mp.	1095
14	empagliflozin.mp.	1246
15	ertugliflozin.mp.	99
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	11245
17	limit 16 to (english language and humans and yr="2018 -Current")	1365
18	limit 17 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	134

Appendix 4: Prior Authorization Criteria

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

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

Length of Authorization:
- Up to 12 months

Requires PA:
- All SGLT-2 inhibitors

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?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of T2DM?	**Yes:** Go to #6	**No:** Go to #4
4. Does the patient have a diagnosis of heart failure with reduced ejection fraction (New York Heart Association class II-IV)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for dapagliflozin 10 mg daily?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~6. Has the patient ~~tried and~~ failed, or have contraindications to, metformin ~~and a sulfonylurea, have contraindications to these treatments~~ or is requesting a SGLT-2 inhibitor to be used in combination with metformin ~~and a sulfonylurea~~? (document contraindication, if any)	**Yes:** Go to #7~~5~~	**No:** Pass to RPh. Deny and recommend trial of metformin ~~or sulfonylurea~~. See below for metformin titration schedule.
~~6.~~7. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <30 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months~~Go to #6~~

Renewal Criteria		
Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <30 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <45 mL/min/ 1.73 m^2 , or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months

Initiating Metformin

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

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

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

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

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

Length of Authorization:
- Up to 12 months

Requires PA:
- GLP-1 receptor agonists that are preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.
- All non-preferred GLP-1 receptor agonists require a PA.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Has the patient tried and failed metformin ~~and sulfonylurea therapy~~ or have contraindications to metformin ~~these treatments~~? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin ~~or sulfonylurea~~. See below for metformin titration schedule.
5. Is the request for semaglutide or dulaglutide?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the patient currently taking prandial insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.	**No:** Approve for up to 12 months

Initiating Metformin

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

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

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

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

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

Length of Authorization:
- Up to 12 months

Requires PA:
- All DPP-4 inhibitors

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Has the patient tried and failed metformin ~~and a sulfonylurea~~, or have contraindications to metformin~~these treatments~~? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin ~~or sulfonylurea~~. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

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

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

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

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Drug Class Update with New Drug Evaluation: Other Dyslipidemia Drugs (non-statin)

Date of Review: August 2020

Generic Name: Bempedoic acid; Bempedoic acid and Ezetimibe

Date of Last Review: May 2019
Dates of Literature Search: 03/01/2019 – 05/31/2020
Brand Name (Manufacturer): Nexletol™; Nexlizet™ (Esperion Therapeutics, Inc.)
Dossier Received: Yes

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

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of non-statin medications for the prevention of cardiovascular (CV) mortality and CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) and high-risk CV patients.
- Analyze the data supporting the efficacy and safety of bempedoic acid and determine its appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for non-statin lipid lowering agents in reducing CV outcomes in patients treated for the primary or secondary prevention of CV disease?
2. Is there new comparative evidence for the safety of non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
3. What are the comparative benefits and harms of bempedoic acid and bempedoic acid/ezetimibe in patients with ASCVD or high-risk CV patients who cannot achieve adequate low-density lipoprotein cholesterol (LDL-C) reduction with their current lipid-lowering regimen?

Conclusions:

- There is no new comparative evidence for the effectiveness or safety of non-statin medications for the prevention of CV mortality and CV events in high risk CV patients.
- There is moderate quality evidence that bempedoic acid modestly lowers LDL-C compared to placebo (17% to 18% placebo-adjusted treatment difference from baseline at week 12) in patients with established CVD on maximally tolerated statin therapy who require additional LDL-C lowering (i.e. LDL ≥ 70 mg/dl).[1,2]
- There is low quality evidence that the combination of bempedoic acid and ezetimibe lowers LDL-C compared to placebo, bempedoic acid monotherapy and ezetimibe monotherapy (treatment difference of -38.2%, -18.9% and -13.5%, respectively).[3]

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- There is insufficient evidence to determine the long-term effectiveness of bempedoic acid or combination bempedoic acid and ezetimibe on clinically meaningful outcomes, including cardiovascular mortality and major adverse cardiovascular events.
- There are several concerning safety signals seen in 52-week trials of bempedoic acid including tendon rupture, gout, nephrolithiasis, and new-onset benign prostatic hypertrophy (BPH). More data are needed to better quantify the risks associated with therapy. Additionally, bempedoic acid resulted in multiple changes to lab parameters during treatment, including increases in serum creatinine, liver transaminases, creatinine kinase and decreases in white blood cell (WBC) count, neutrophils and hemoglobin.

Recommendations:

- Due to its unknown benefit on CV outcomes and multiple safety concerns, maintain bempedoic acid and bempedoic acid/ezetimibe as non-preferred.
- Include prior authorization to limit utilization to high-risk CV patients requiring additional LDL-lowering on maximally tolerated statin therapy and ezetimibe. (**Appendix 4**).
- Update prior authorization to include new FDA approved indication for icosapent ethyl (**Appendix 4)**.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

- Current PA polices for PCKS9 inhibitors and omega-3 fatty acids are included in **Appendix 4.**
- There is moderate quality evidence that ezetimibe combined with a statin results in a modest (2%) improvement in CV outcomes with a long duration of follow-up (approximately 7 years).[4]
- Moderate quality evidence comparing statin monotherapy to a statin in combination with niacin, fibrates or omega 3 fatty acids shows no significant effect on reducing all-cause mortality, death from coronary heart disease (CHD) and inconsistent effects on other CV outcomes.
- There is low quality evidence that high dose icosapent ethyl (2 gm twice daily) may prevent a CV event (17.2% vs. 22.2%; HR 0.75; 95% CI 0.68 to 0.83; ARR 4.8%; NNT 21 over 4.9 years) in patients with hypertriglyceridemia and CV disease or with diabetes plus other CV risks on statin therapy.[5] However, this is inconsistent with prior studies and meta-analysis that have not shown a CV benefit with omega-3 fatty acids. Additionally, there are serious limitations to the study including the use of mineral oil as placebo, the disconnect between the modest triglyceride lowering seen and greater than predicted CV benefit, as well as significant funding and involvement in the study oversight and data interpretation by the manufacturer. More data are needed to confirm these findings and icosapent ethyl remains non-preferred.
- There is high quality evidence of a decrease in CV events with alirocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.5% vs. 11.1%; hazard ratio [HR] 0.85; 95% CI 0.78 to 0.93; absolute risk reduction [ARR] 1.6%; number-needed-to-treat [NNT] 63) and moderate quality evidence of lower risk of overall mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.99), but no significant difference in death due to CV causes (2.5% vs. 2.9%).[6]
- There is high quality evidence of a similar decrease in CV events with evolocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; ARR 1.5%; NNT 67). The incidence of death from any cause was similar between groups after 26 months (3.2% vs. 3.1%; HR 1.04; 95% CI 0.91 to 1.19).[7]
- Evolocumab and alirocumab currently require prior authorization for approval to limit use to patients with CVD or familial hypercholesterolemia at high risk for CV events who require additional LDL-C lowering despite use of other lipid-lowering agents, including statins.

Background:

The association between hypercholesteremia, and particularly elevated low-density lipoprotein (LDL) cholesterol, and cardiovascular disease (CVD) is well established. In addition to optimizing a healthy lifestyle, prevention of ASCVD events involves optimization of treatments that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until more recently, only statins had strong and consistent evidence demonstrating ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment for both primary and secondary prevention of ASCVD. However, combination or non-statin therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations.

The utilization and place in therapy of non-statin therapy has significantly evolved over the past few decades from being routine add on therapy targeting specific LDL-C goals to having no clear indication based on a lack of data showing an improvement on CV outcomes. The recent publication of the 2018 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol once again re-define the role of non-statin therapy.[8] A consistent approach is to reserve non-statin add-on therapy to high risk populations on maximally tolerated statin therapy who may require additional LDL-C lowering and to use agents which have demonstrated an improvement in CV outcomes. The updated guidelines consider an LDL-C threshold of 70 mg/dl reasonable to add a non-statin agent in those with clinical ASCVD. [8]

Currently, only ezetimibe, icosapent ethyl and the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have shown a modest benefit on clinical outcomes of interest when added to statin therapy (**Tables 1 and 2**). Ezetimibe, an inhibitor of intestinal cholesterol absorption, is indicated as an adjunct to reduce elevated cholesterol and LDL-C.[9] It is generally well tolerated and can lower LDL-C by up to 25% when added to statin therapy. The IMPROVE-IT trial provides modest evidence for use of ezetimibe in combination with a statin for secondary prevention of CV events.[4] In patients with recent acute coronary syndrome (ACS), ezetimibe produced an incremental reduction in the primary composite endpoint, and specifically reduced nonfatal ischemic stroke, but did not reduce all-cause mortality or CV mortality. The manufacturer of ezetimibe applied for an additional indication for the expanded use of ezetimibe in combination with statin therapy for reduction of CV events in patients with coronary heart disease, but an FDA advisory committee voted against the expanded indication as they felt the ezetimibe/simvastatin combination provides a weak and not particularly robust effect on CV outcomes.[9] Additionally, a moderate-intensity statin was used as the study comparator, which is not consistent with current practice recommendations.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[10,11] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and clinical ASCVD who require additional lowering of LDL-C. Additionally, they are both FDA approved for the risk reduction of MI, stroke, and coronary revascularization in adults with established CVD based on clinical outcome data from the FOURIER and ODYSSEY OUTCOMES trial **(Tables 1 and 2).**[7,10] [6] Icosapent ethyl is an ethyl ester of EPA (eicosapentaenoic acid) without any DHA (docosahexaenoic acid). The REDUCE-IT trial suggests it may prevent a CV event in high-risk CV patients (NNT 21) over 5 years.[5] This is in patients with elevated triglycerides despite statin therapy. Icosapent ethyl gained FDA approval as an add-on therapy to reduce CV events for adults with elevated triglycerides ($\geq$ 150 mg/dl) in December 2019. This is conflicting with data with lower doses or other omega-3 fatty acids. Furthermore, icosapent ethyl can cause atrial fibrillation (NNH 71) and may increase the risk of bleeding. [5]

Currently there is no evidence on CV outcomes and a limited place in therapy for other LDL-C lowering agents (fibrates, bile acid sequestrants, omega-3 fatty acids). Fibric acid derivatives should be reserved for patients with severe hypertriglyceridemia (triglycerides ≥ 500 to 1000 mg/dl). The long-term follow up of the

ACCORD trial showed no benefit in fatal or non-fatal CV events with fenofibrate plus simvastatin versus simvastatin alone in patients with diabetes mellitus.[12] Gemfibrozil should not be used in combination with statin therapy due to an increased risk of muscle symptoms and rhabdomyolysis. Omega-3 fatty acids (i.e. Lovaza®) other than icosapent ethyl have not shown a consistent benefit in the primary or secondary prevention of CV outcomes in a recent large-scale clinical trial.

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[4-7]

	FOURIER	ODYSSEY	IMPROVE-IT	REDUCE-IT
Non-Statin Study Drug	Evolocumab	Alirocumab	Ezetimibe	Icosapent ethyl 2 gm BID
Patient Population	MI, CVA or PAD	4-52 weeks post-ACS	ACS (prior 10 days)	CVD or DM and ≥ risk factor with TG ≥ 150 mg/dl
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl	75 mg/dl (median TG 2116 mg/dl)
% on High Intensity Statin	69%	89%	6%	30%
% on Ezetimibe	5%	3%	100%	6.5%
Study Duration	26 months	34 months	6 years	5 years

Abbreviations: ACS: acute coronary syndrome: BID: twice daily; CVA: cerebrovascular accident; CVD: cardiovascular disease; DM: diabetes mellitus; LDL-C: low density lipoprotein cholesterol MI: myocardial infarction; PAD: peripheral artery disease; TG: triglyceride

Table 2: Summary of Results from Cardiovascular Outcome Trials[4-7]

Outcome	Evolocumab ARR/NNT	Alirocumab ARR/NNT	Ezetimibe ARR/NNT	Icosapent ARR/NNT
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50	4.8% / 21
CV Death	NS	NS	NS	0.9% / 112
Death from any cause	NS	0.6% / 167	NS	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59	2.3% / 44
Stroke	0.4% / 250	0.4% / 250	NS	0.8% / 125

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: not significant

Methods:

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

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

Systematic Reviews:
A systematic review included RCTs comparing PCSK9 inhibitors with placebo or lipid-lowering therapy evaluating all-cause mortality and major adverse cardiovascular events (MACE).[13] A total of 23 trials (n=88,041) with low risk of bias were included in the analysis evaluating alirocumab (n=16), evolocumab (n=5) and bococizumab (n=2). The majority of trials (14) involved secondary prevention of CVD, but studies in primary prevention (n=9) were also included. PCSK9 inhibitors were not associated with a reduction in either all-cause mortality (OR 0.91; 95% CI 0.78 to 1.06) or CV deaths (OR 0.95; 95% CI 0.84 to 1.07). [13] Treatment with a PCSK9 inhibitor was associated with a reduction in MACE (OR 0.82; 95% CI 0.77 to 0.87) and myocardial infarction (MI) (0.80; 95% CI 0.71 to 0.91). [13] Mega-regression showed that the benefit was not impacted by LDL-C, age and duration of follow up. There was heterogeneity in the included population, since both subjects with CVD and high-risk primary prevention patients were included. Longer term follow up may be necessary for a mortality reduction to be seen.

A systematic review and meta-analysis evaluated RCTs (n=11) comparing omega 3 fatty acids in adults experiencing a MI within 6 weeks.[14] Six of the trials were found to have moderate or high risk of bias due to incomplete blinding, allocation concealment and attrition bias. There was no statistically significant reduction in all-cause mortality (RR 0.86; 95% CI 0.72 to 1.02), but there was a reduction in CV mortality (RR 0.77; 95% CI 0.65 to 0.91) and recurrent MI (RR 0.77; 95% CI 0.6 to 0.99) in patients with a recent MI.[14] There was no significant reduction in any clinical outcomes when including only trials with low risk of bias which makes the overall pooled estimates difficult to interpret.

New Guidelines:
None identified

New Formulations or Indications:
In April 2019, alirocumab was FDA approved to reduce the risk of MI, stroke and unstable angina in adults with established CVD. This approval was based on the ODYSSEY OUTCOMES trial which was evaluated in a previous review.[14] This study demonstrated a 1.6% absolute risk reduction over 3 years in a composite of coronary heart disease (CHD) death, MI, ischemic stroke and unstable angina in adults with ACS 1-12 months prior.

In December 2019, FDA expanded the label for icosapent ethyl as adjunct to statin therapy to reduce the risk of MI, stroke, coronary revascularization and unstable angina in adults with TG levels ≥ 150 mg/dL based on the REDUCE-IT trial.[5] This data were reviewed in a previous update.

New FDA Safety Alerts:
None identified

Randomized Controlled Trials:
A total of 7 citations were manually reviewed from the initial literature search.[15-21] After further review, all were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C.[22]

Bempedoic acid was approved based on two pivotal secondary prevention trials in high risk patients including those with clinical ASCVD or heterozygous familial hypercholesterolemia (HeFH) on maximally tolerated statin therapy (**Table 5**) (CLEAR Harmony and CLEAR Wisdom).[1,2] Both were 52-week randomized, double-blind trials comparing bempedoic acid to placebo in patients on baseline lipid-modifying therapy with LDL ≥ 70 mg/dl. Study design and inclusion/exclusion criteria were similar (**Table 5**). However, in CLEAR Wisdom, a 4-week run in period for statin optimization and compliance was included.[1] The majority of patients in both trials had established ASCVD (~95%) and data in those with HeFH is limited (<5% of subjects). While the majority of patients were on statin therapy, only half of patients were on the recommended high intensity dosing.

Both trials resulted in a significant reduction in LDL-C from baseline at week 12 compared to placebo (treatment difference -18.1%; 95% CI -20 to -16.1% in CLEAR Harmony and -17.4%; 95% CI -21 to -13.9% in CLEAR Wisdom). [1,2] LDL lowering was consistent across subgroups, including baseline CV risk, baseline LDL, baseline lipid-lowering therapy, and baseline statin intensity. However, the effect was smaller in subjects on background statins Significant reductions in non-HDL cholesterol, total cholesterol, apolipoprotein B and high-sensitivity C-reactive protein were also observed. There were minimal effects on triglycerides (TG). The magnitude of LDL-lowering is similar to observations of ezetimibe when added to statin therapy (-13 to -20%) and lower than what is seen from the PCSK9 inhibitors (-47% to -63% additional lowering). Additionally, the efficacy was reduced after week 12, but still remained statistically superior to placebo at week 52.

Both trials had significant exclusion criteria **(Table 5)** and a high percentage of screen failures (34.3% in CLEAR Harmony and 66.1% in CLEAR Wisdom) during the run-in and/or screening periods. [1,2] Therefore, there are substantial concerns with external validity and generalizability of these results.

Two additional supportive phase 3 trials included primary and secondary prevention patients with hyperlipidemia who were considered statin-intolerant.[23,24] Patients were on either no statin, very-low-dose statin or low-dose statin and ezetimibe. Both trials included a 4-week placebo run-in period for compliance with a high percentage of screening failures (42.7% and 56.3%), limiting generalizability of these results. In one of the supportive trials, more bempedoic acid treated patients discontinued due to adverse events compared to placebo (2.6% vs. 0.9%, respectively). [23,24] Most patients were enrolled for primary prevention and mean baseline LDL-C values were 157.6 mg/dl and 127.6 mg/dl. More than half of patients were not on any lipid lowering therapy (50% and 58%). Bempedoic acid resulted in a significant reduction in LDL-C from baseline compared to placebo in both trials (treatment difference -21%; 95% CI -25.0% to -17.0% and -28.6%; 95% CI -34.9% to -22.4%).[23,24] Overall, there was a larger reduction in LDL-C in those who were not on statin therapy at baseline.

The combination of bempedoic acid 180 mg and ezetimibe 10 mg was also FDA approved as adjunct to maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C.[3] Approval was based on one 12-week RCT (**Table 5**) with unclear risk of bias comparing the combination of bempedoic acid/ezetimibe to each individual drug and active placebo in patients with ASCVD, HeFH or high risk CV patients

(primary prevention) on maximally tolerated statin therapy. Three of the study sites were found to have data irregularities indicating possible fraud and data from these sites were excluded from the post hoc efficacy and safety analysis and from the FDA analysis.[25] The FDA review notes that the trial was adequately powered despite exclusion of this data and exclusion did not introduce any additional bias.[25]

Approximately 60% of patients had ASCVD or HeFH and 40% were primary prevention patients with CV risk factors.[3] However, only 65% were on maximally tolerated statin therapy and approximately 21% were on high intensity statins. The FDA review suggests that the enrolled patient population did not adequately reflect the intended clinical population due to the low rates of adequate treatment at baseline. [25] Additionally, over half of patients screened did not meet the randomization criteria.

Overall, there was a statistically significant reduction in LDL-C with the combination of bempedoic acid and ezetimibe compared to the individual drug components and placebo, demonstrating that both agents contribute to the drug's treatment effect. The placebo-adjusted treatment difference in LDL-C at week 12 for the combination, bempedoic acid, and ezetimibe was -38.2%, -19.3% and -24.7%, respectively (**Table 5**).[3] Ezetimibe appears to contribute to the treatment effect more than bempedoic acid and the treatment effect was larger than expected based on the previous studies of bempedoic acid monotherapy. This may be due to different patient populations (mix of primary and secondary prevention) and higher baseline LDL-C values than the pivotal bempedoic acid subjects.

None of the clinical trials were designed or powered to evaluate the effects of bempedoic acid on CV outcomes. Until further data is available on clinically important outcomes, statin therapy should be optimized in patients with CV disease and HeFH. In high risk patients requiring additional LDL-lowering therapy, non-statin agents (i.e. ezetimibe) with some potential CV benefit and more safety data should be prioritized.

Clinical Safety:

In the pivotal trials, there were significantly more discontinuations due to adverse events in the bempedoic group compared to placebo (10.9% vs. 7.5%).[26] The incidence of muscle-related adverse events was similar in the two groups. The most common reasons for discontinuation were diarrhea, musculoskeletal pain, elevated liver enzymes, other gastrointestinal symptoms and headache. More patients on bempedoic experienced gout (1.5%) compared to placebo (0.4%), increases in serum uric acid (3.5% vs. 1.1%), tendon rupture (0.5% vs. 0%) and new-onset BPH in men (1.3% vs. 0.1%).[26] Bempedoic acid competes for the same renal transporters as uric acid and therefore can increase uric acid levels. Adverse effects occurring at higher rates than placebo are included in **Table 3**.

Table 3: Adverse Events Occurring at 0.5% Higher Frequency in Treatment Arm compared to Placebo[26]

	Bempedoic Acid (n=2009) N(%)	Placebo (n=999) N(%)
Upper respiratory tract infection	91 (4.5)	40 (4.0)
Muscle spasms	73 (3.6)	23 (2.3)
Increased uric acid	70 (3.5)	11 (1.1)
Back pain	66 (2.2)	22 (2.2)
Pain in extremity	61 (3.0)	17 (1.7)
Anemia	57 (2.8)	19 (1.9)

Elevated liver enzymes	44 (2.2)	10 (1.0)
Abdominal pain	39 (1.9)	14 (1.4)
Atrial fibrillation	34 (1.7)	11 (1.1)
Gout	31 (1.5)	4 (0.4)
Vomiting	27 (1.3)	2 (0.2)
Increases in Scr/Decreases in eGFR	27 (1.3)	4 (0.4)
Renal insufficiency	18 (0.9)	1 (0.1)
Benign prostatic hyperplasia	18 (0.9)	3 (0.3)

In the pivotal RCTs, there was an imbalance in total deaths, with 25 deaths in the bempedoic acid group (1.2%) compared to 8 in the placebo group (0.8%).[26] The death imbalance appears to be driven by malignancy-associated deaths.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) All-cause and CV mortality
2) Fatal and non-fatal CV events
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percent change from baseline to Week 12 in LDL-C

Table 4. Pharmacology and Pharmacokinetic Properties

Parameter	
Mechanism of Action	Bempedoic acid is a prodrug metabolized in the liver to an active adenosine triphosphate-citrate lyase inhibitor that lowers LDL-C by inhibition of cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.
Oral Bioavailability	~70%
Distribution and Protein Binding	18 L. 99% protein bound.
Elimination	70% recovered in urine (primarily as acyl glucuronide metabolite), 30% recovered in feces. <5% excreted as unchanged bempedoic acid.
Half-Life	21 hours
Metabolism	<2% renal clearance. Primary route is through metabolism of the acyl glucuronide.

Abbreviations:

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/NNH	Risk of Bias/ Applicability
1. Ray, et al. CLEAR Harmony[2] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg daily 2. Placebo 52 weeks duration	Demographics: •Mean age 66 •27% Female •96% white •71% DM •97% ASCVD •3.5% HeFH •50% High intensity statin at baseline •9% ezetimibe •Mean LDL 103 mg/dl Key Inclusion Criteria: •≥ 18 years, nonpregnant •LDL-C ≥ 70 mg/dl •HeFH OR ASCVD •On maximally tolerated statin +/- other lipid lowering therapies Key Exclusion Criteria: •TG ≥ 500 mg/dl •eGFR < 30 ml/min •BMI ≥ 50 kg/m2 •Use of PCSK9 inhibitors •Recent ACS (within 3 months) •SBP ≥ 160 mm Hg •HgA1C ≥ 10% •Liver dysfunction, HCV, HBV •Hgb < 10 g/dl •Active malignancy •CK > 3 x ULN •Drug, alcohol abuse	ITT: 1. 1488 2. 742 PP: 1. 1404 2. 706 Attrition: 1. 84 (5.7%) 2. 36 (4.9%)	Change in LDL-C from baseline to week 12 1. -19.2 mg/dl (-16.5%) 2. 0.2 mg/dl (1.6%) Difference -18.1%; 95% CI -20 to -16.1); p<0.001	N/A	Discontinuation due to AE: 1. 162 (10.9%) 2. 53 (7.1%) P=0.005 Serious AE 1. 216 (15.4%) 2. 104 (14%) NS Major adverse cardiac event 1. 68 (4.6%) 2. 42 (5.7%) NS	ARI 3.8% / NNH 27 NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; groups similar at baseline. Randomization and allocation concealment through Interactive Web-based Response System. Performance Bias: low; double-blind, matching placebo Detection Bias: low; blinded clinical events committee adjudicated clinical outcomes Attrition Bias: unclear; majority of patients completed the study in each group (~95%) but high rates of treatment discontinuation in treatment (23.2%) and placebo group (19.1%). Missing lipid values were imputed based on observed values in their randomized treatment group Reporting Bias: low; outcomes reported as specified Other Bias: high; funded by Esperion Therapeutics which was involved in trial design, data collection and analysis and manuscript development. **Applicability**: Patient: Significant exclusion criteria and screening period limits generalizability to real world patients. 34.4% (n=1165) of screened patients were not randomized due to failure to meet criteria or withdrawal Intervention: 180 mg demonstrates maximal LDL-lowering in dose-ranging studies with no significant increase in dose-related laboratory changes (Scr, uric acid, Hg, BUN) Comparator: Placebo. Active comparator (i.e ezetimibe) lacking Outcomes: LDL-C is a surrogate outcome. Not powered or designed to evaluate CV outcomes. Setting: Multicenter in 5 countries (U.S., Canada, Germany, Netherlands, Poland, U.K). 65% Europe and 34% North America (25% U.S.)

2. Goldberg et al CLEAR Wisdom[1] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg daily 2. Placebo 52 weeks duration	Demographics: • Mean age 64 •35% Female •95% white •70% DM •94% ASCVD •5% HeFH •53% High intensity statin at baseline •8% ezetimibe •Mean LDL 120 mg/dl Key Inclusion Criteria: See Ray et al Key Exclusion Criteria: See Ray et al PLUS Noncompliance with 4-week placebo run-in	ITT: 1. 522 2. 257 PP: 1. 490 2. 250 Attrition: 1. 32 (6.1%) 2. 7 (2.7%)	Change in LDL-C from baseline to week 12 1. -15.1% 2. 2.4% Difference -17.4%; 95% CI -21 to -13.9%); p<0.001	N/A	Discontinuation due to AE: 1. 57 (10.9%) 2. 22 (8.6%) *p-value not provided Serious AE 1. 106 (20.3%) 2. 48 (18.7%) NS Major adverse cardiac event 1. 43 (8.2%) 2. 26 (10.1%) RR 0.81; 95% CI 0.51 to 1.29	N/A* NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; groups similar at baseline. Randomization and allocation concealment through Interactive Web-based Response System. Performance Bias: low; double-blind, matching placebo Detection Bias: low; blinded clinical events committee adjudicated clinical outcomes Attrition Bias: unclear; More patients in the treatment group withdrew from the study and discontinued drug. Reporting Bias: low; outcomes reported as specified Other Bias: high; funded by Esperion Therapeutics which was involved in trial design, data collection and analysis and manuscript development **Applicability**: Patient: Significant exclusion criteria and a 4-week placebo run-in period for statin optimization and compliance prior to randomization limits generalizability. 66.1% of patients screened failed to enter the randomization process for not meeting criteria or withdrawal. Intervention: See Ray et al Comparator: See Ray et al Outcomes: See Ray et al Setting: Multicenter (86 sites in 6 countries) 71% Europe, 29% North America (27% U.S)

3. Ballantyne et al.[3] DB, PC, MC, RCT	1. Bempedoic Acid 180 mg/ ezetimibe 10 mg daily 2. Bempedoic Acid 180 mg 3. Ezetimibe 10 mg 4. placebo 12 weeks duration	Demographics: •60% ASCVD or HeFH •40% with CV Risk factors •Mean LDL 146-152 mg/dl •65% on maximally tolerated statin •28% on no therapy Key Inclusion Criteria: •≥ 18 years •LDL-C ≥ 100 mg/dl (ASCVD) or 130 mg/dl (CV risk factors) •HeFH OR ASCVD or multiple CVD risk factors •On maximally tolerated statin • Key Exclusion Criteria: •TG ≥ 500 mg/dl •eGFR < 30 ml/min •BMI ≥ 40 kg/m2 •Use of PCSK9 inhibitors, fibrates, niacin, bile acid sequestrants •Recent ACS (within 3 months) •SBP ≥ 160 mm Hg •HgA1C ≥ 10% •Liver dysfunction, HCV, HBV •Hgb < 10 g/dl •Active malignancy •CK > 3 x ULN •Drug, alcohol abuse	ITT: 1. 108 2. 110 3. 109 4. 55 FAS* 1. 86 2. 88 3. 86 4. 41 PP*: 1. 81 2. 82 3. 81 4. 40 Attrition: 1. 5 (5.8%) 2. 6 (6.8%) 3. 5 (5.8%) 4. 1 (2.4%) *Excluding 3 clinical sites with unreliable data	Change in LDL-C from baseline to week 12 1. -36.2% 4. 2.0% Treatment difference -38.2% 95% CI -46.9 to -29.4) P<0.001 1. -36.2% 2. -17.3% Treatment difference -18.9% 95% CI -26.3 to -11.5) P<0.001 1. -36.2% 3. -22.7% Treatment difference -13.5% 95% CI -20.6 to -6.3) P<0.001	N/A	Discontinuation due to AE: 1. 7 (8.2%) 2. 9 (10.2%) 3. 10 (11.6) 4. 2(4.9) P values not provided Serious AE 1. 8 (9.4%) 2. 7 (8%) 3. 9 (10.5%) 4. 1 (2.4%) P values not provided	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; unclear randomization and allocation concealment methods. Patients in the combination group were younger, more obese and had higher baseline TGs. Performance Bias: low; double-blind, matching placebo Detection Bias: unclear; unclear blinding of outcome assessors Attrition Bias: unclear; majority of patients completed the study in each group (~95%) but slight differences in each group and higher rates of study discontinuation (11-15%). Additional attrition from exclusion of 3 clinical sites. Reporting Bias: unclear; Fraudulent data identified at 3 clinical sites in which subjects in active study drug groups who reported ingestion of study drug had no detectable study drug in samples. Data from these 3 sites were excluded from the analysis (n=81) Other Bias: high; funded by Esperion pharmaceuticals. **Applicability**: Patient: 54% of screened patients were not randomized due to reasons unknown. Lower number of subject on baseline statin therapy than expected in clinical practice could inflate LDL-C lowering effects. Intervention: 180 mg demonstrates maximal LDL-lowering in dose-ranging studies with no significant increase in dose-related laboratory changes (Scr, uric acid, Hgb, BUN) Comparator: No concerns Outcomes: LDL-C is a surrogate outcome. Not powered or designed to evaluate CV outcomes. Setting: Multicenter (78 sites) in the U.S.

Abbreviations [alphabetical order]: ACS = acute coronary syndrome; AE = adverse events; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BUN = blood urea nitrogen; CI = confidence interval; CK = creatinine kinase; CV = cardiovascular; DM = diabetes mellitus; HBV = hepatitis B virus; HCV = hepatitis C virus; HeFH = heterozygous familial hypercholesterolemia; HgA1C = hemoglobin A1C; Hgb = hemoglobin; ITT = intention to treat; mITT = modified intention to treat; LDL = low density lipoprotein; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SBP = systolic blood pressure; SCr = serum creatinine; TG = triglycerides; ULN = upper limit of normal

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	POWDER	Y
cholestyramine/aspartame	PREVALITE	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	POWDER	Y
evolocumab	REPATHA SURECLICK	PEN INJCTR	Y
evolocumab	REPATHA SYRINGE	SYRINGE	Y
evolocumab	REPATHA PUSHTRONEX	WEAR INJCT	Y
ezetimibe	EZETIMIBE	TABLET	Y
ezetimibe	ZETIA	TABLET	Y
fenofibrate	FENOFIBRATE	TABLET	Y
alirocumab	PRALUENT PEN	PEN INJCTR	N
colesevelam HCl	COLESEVELAM HCL	POWD PACK	N
colesevelam HCl	WELCHOL	POWD PACK	N
colesevelam HCl	COLESEVELAM HCL	TABLET	N
colesevelam HCl	WELCHOL	TABLET	N
colestipol HCl	COLESTID	GRANULES	N
colestipol HCl	COLESTIPOL HCL	GRANULES	N
colestipol HCl	COLESTID	PACKET	N
colestipol HCl	COLESTIPOL HCL	PACKET	N
colestipol HCl	COLESTID	TABLET	N
colestipol HCl	COLESTIPOL HCL	TABLET	N
fenofibrate	FENOFIBRATE	CAPSULE	N
fenofibrate	LIPOFEN	CAPSULE	N
fenofibrate	FENOFIBRATE	TABLET	N
fenofibrate	FENOGLIDE	TABLET	N
fenofibrate nanocrystallized	FENOFIBRATE	TABLET	N
fenofibrate nanocrystallized	TRICOR	TABLET	N
fenofibrate nanocrystallized	TRIGLIDE	TABLET	N
fenofibrate,micronized	ANTARA	CAPSULE	N
fenofibrate,micronized	FENOFIBRATE	CAPSULE	N
fenofibric acid	FENOFIBRIC ACID	TABLET	N
fenofibric acid	FIBRICOR	TABLET	N

fenofibric acid (choline)	FENOFIBRIC ACID	CAPSULE DR	N
fenofibric acid (choline)	TRILIPIX	CAPSULE DR	N
gemfibrozil	GEMFIBROZIL	TABLET	N
gemfibrozil	LOPID	TABLET	N
icosapent ethyl	VASCEPA	CAPSULE	N
inositol	INOSITOL	TABLET	N
inositol	INOSITOL	TABLET	N
lomitapide mesylate	JUXTAPID	CAPSULE	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN ER	TAB ER 24H	N
niacin	NIASPAN	TAB ER 24H	N
niacin	NIACIN	TABLET	N
niacin	NIACIN	TABLET	N
niacin	NIACOR	TABLET	N
niacin	NIACIN	TABLET ER	N
niacin	SLO-NIACIN	TABLET ER	N
omega-3 acid ethyl esters	LOVAZA	CAPSULE	N
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	CAPSULE	N
choline	CHOLINE	TABLET	
niacin	NIACIN	TABLET ER	
niacin	NIACIN	TABLET ER	
niacin	NIADELAY	TABLET ER	
niacin	SLO-NIACIN	TABLET ER	
niacin (inositol niacinate)	NIACIN INOSITOL	CAPSULE	
niacinamide	NIACINAMIDE	TABLET	
niacinamide	NIACINAMIDE	TABLET	

Appendix 2: Medline Search Strategy

Database: Ovid MEDLINE(R) <2019 to May Week 4 2020>

Search Strategy:

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1 (Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or alirocumab or evolocumab or psck9 inhibitors).af. (38939)

2 (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases).af. (457555)

3 ((Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors) and (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases)).af. (4436)

4. to (english language and humans and yr="2019 -Current" and (clinical trial, all or clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) (23)

Appendix 3: Prescribing Information Highlights

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

NEXLETOL (bempedoic acid) tablets, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
NEXLETOL is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. (1)

Limitations of Use: The effect of NEXLETOL on cardiovascular morbidity and mortality has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------
Administer 180 mg orally once daily with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 180 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
- *Hyperuricemia*: Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. (5.1)
- *Tendon Rupture:* Tendon rupture has occurred. Discontinue NEXLETOL at the first sign of tendon rupture. Avoid NEXLETOL in patients who have a history of tendon disorders or tendon rupture. (5.2)

----------ADVERSE REACTIONS----------
Most common (incidence ≥ 2% and greater than placebo) adverse reactions are upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Esperion at 833-377-7633 (833 ESPRMED) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- *Simvastatin:* Avoid concomitant use of NEXLETOL with simvastatin greater than 20 mg. (7)
- *Pravastatin:* Avoid concomitant use of NEXLETOL with pravastatin greater than 40 mg. (7)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy*: Based on mechanism of action, may cause fetal harm. (8.1)
- *Lactation*: Breastfeeding is not recommended with NEXLETOL. (8.2)

SEE 17 FOR PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

REVISED: 02/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NEXLIZET (bempedoic acid and ezetimibe) tablets, for oral use
Initial U.S. Approval: 2020

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

NEXLIZET, which contains an adenosine triphosphate-citrate lyase (ACL) inhibitor and a cholesterol absorption inhibitor, is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. (1)

Limitations of Use: The effect of NEXLIZET on cardiovascular morbidity and mortality has not been determined. (1)

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

- Administer one tablet (180 mg bempedoic acid and 10 mg ezetimibe) orally once daily with or without food. (2.1)
- Swallow the tablet whole. (2.1)
- Coadministration with Bile Acid Sequestrants: Administer at least 2 hours before or at least 4 hours after bile acid sequestrants. (2.2, 7)

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

Tablets: 180 mg bempedoic acid/10 mg ezetimibe (3)

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

- Known hypersensitivity to ezetimibe tablets. (4, 6.2)

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

- *Hyperuricemia*: Elevations in serum uric acid have occurred. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. (5.1)
- *Tendon Rupture:* Tendon rupture has occurred. Discontinue NEXLIZET at the first sign of tendon rupture. Avoid NEXLIZET in patients who have a history of tendon disorders or tendon rupture. (5.2)

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

Most common (incidence ≥2% and greater than placebo) adverse reactions are upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Esperion at 833-377-7633 (833 ESPRMED) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- Simvastatin: Avoid concomitant use of NEXLIZET with simvastatin great than 20 mg. (7)
- *Pravastatin:* Avoid concomitant use of NEXLIZET with pravastatin greater than 40 mg. (7)
- *Cyclosporine:* Monitor cyclosporine concentrations. (7)
- *Fibrates:* If cholelithiasis is suspected in a patient receiving NEXLIZET and fenofibrate, consider alternative lipid-lowering therapy. (6.2, 7)

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

- *Pregnancy*: Based on mechanism of action, may cause fetal harm. (8.1)
- *Lactation*: Breastfeeding is not recommended with NEXLIZET. (8.2)

SEE 17 FOR PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

REVISED: 02/2020

PCSK9 Inhibitors

Goal(s):

- Promote use of PCSK9 inhibitors that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 inhibitors

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 the renewal of a previously approved prior authorization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) <u>Major ASCVD events</u> • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease <u>High-Risk Conditions:</u> • Age ≥ 65 • Heterozygous familial hypercholesterolemia • History of prior CABG or PCI • Diabetes Mellitus • Hypertension • Chronic Kidney Disease • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 3 months with a LDL-C still ≥ 70 mg/dl? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C	**Yes:** Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ mg/dL Date:_____ Recent LDL-C _____ mg/dL Date:_____	**No:** Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
6. Does the patient have: • A history of rhabdomyolysis caused by a statin; or alternatively, • a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin; or • Intolerable statin-associated side effects that have been re-challenged with ≥ 2 statins Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #8	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.

Renewal Criteria	
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2

Renewal Criteria		
2. Is the patient adherent with PCSK9 inhibitor therapy?	**Yes:** Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 12 months)	**No:** Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

P&T / DUR Review: *5/19 (MH); 1/18; 11/16; 11/15*
Implementation: *7/1/2019; 3/1/18; 1/1/1*

Omega-3 Fatty Acids

Goal(s):

- Restrict use of non-preferred omega-3 fatty acids to patients at increased risk for pancreatitis.
- Promote use of agents that have demonstrated a substantial benefit on cardiovascular outcomes that is consistent with medical evidence

Length of Authorization:

- Up to 12 months

Requires PA:

- Omega-3-Acid Ethyl Esters (Lovaza®)
- Icosapent Ethyl (Vascepa®)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at a maximum tolerable dose (as seen in dosing table below); **OR** Is the patient taking a statin and unable to take a fibric acid derivative due to an increased risk of myopathy?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of other agent(s).
6. Is the prescription for icosapent ethyl?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have established clinical atherosclerotic cardiovascular disease (ASCVD), (defined as documented history of acute coronary syndrome, ischemic stroke, peripheral artery disease, coronary artery disease) or type 2 diabetes mellitus and ≥ 2 CV risk factors?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Does the patient have triglycerides greater than or equal to 150 mg/dl while on maximally tolerated statin treatment?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Dosing of Fenofibrate and Derivatives for Hypertriglyceridemia.

Trade Name (generic)	Recommended dose	Maximum dose
Antara (fenofibrate capsules)	43-130 mg once daily	130 mg once daily
Fenoglide (fenofibrate tablet)	40-120 once daily	120 mg once daily
Fibricor (fenofibrate tablet)	25-105 mg once daily	105 mg once daily
Lipofen (fenofibrate capsule)	50-150 mg once daily	150 mg once daily
Lofibra (fenofibrate capsule)	67-200 mg once daily	200 mg once daily
Lofibra (fenofibrate tablet)	54-160 mg once daily	160 mg once daily
Lopid (gemfibrozil tablet)	600 mg twice daily	600 mg twice daily
Tricor (fenofibrate tablet)	48-145 mg once daily	145 mg once daily
Triglide (fenofibrate tablet)	50-160 mg once daily	160 mg once daily
Trilipix (fenofibrate DR capsule)	45-135 mg once daily	135 mg once daily

Bempedoic Acid

Goal(s):

- Promote use of bempedoic acid that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- Up to 12 months

Requires PA:

- Bempedoic Acid (Nexletol™)
- Bempedoic acid and ezetimibe (Nexlizet™)

Covered Alternatives:

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

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code; go to #2

Approval Criteria		
2. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) <u>Major ASCVD events</u> • Recent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease <u>High-Risk Conditions:</u> • Age ≥ 65 • Heterozygous familial hypercholesterolemia • History of prior CABG or PCI • Diabetes Mellitus • Hypertension • Chronic Kidney Disease • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure	**Yes:** Go to #3	**No:** Go to #6

Approval Criteria		
3. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 3 months with a LDL-C still ≥ 70 mg/dl? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C	**Yes:** Confirm documentation; go to #4 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ Date:_____ Recent LDL-C _____ Date:_____	**No:** Go to #5
4. Is the patient adherent with a high-intensity statin and ezetimibe?	**Yes:** Go to #8 Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	**No:** Pass to RPh; deny for medical appropriateness
5. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	**Yes:** Confirm chart documentation of diagnosis or labs and Go to #8 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness

Approval Criteria		
6. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness.
7. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe?	**Yes:** Go to #8 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient have a history of gout or hyperuricemia?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Approve for up to 12 months

High- and Moderate-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Pitavastatin 1-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

P&T / DUR Review: 08/20
Implementation:

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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OHSU Drug Effectiveness Review Project Summary Report – Disease-Modifying Drugs for Multiple Sclerosis

Date of Review: August 2020

Date of Last Review: November 2017
Literature Search: 01/01/16 - 2/3/2020

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

Purpose for Class Update:
This review examines new comparative evidence of disease modifying drugs (DMDs) for multiple sclerosis (MS) published since 2017 and summarizes the evidence for 3 new DMDs approved to treat MS; cladribine, ozanimod, and siponimod, as presented in a 2020 Drug Effectiveness Review Project (DERP) systematic review focused on MS.

Research Questions:
1. What is the comparative effectiveness of DMDs for MS?
2. What is the comparative effectiveness of DMDs for clinically isolated syndrome (CIS)?
3. Do DMDs for MS or CIS differ in harms?
4. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?

Conclusions:
- Since the last review, 4 new oral MS drugs have received Food and Drug Administration (FDA) approval: monomethyl fumarate, ozanimod, cladribine, and siponimod. Dimethyl fumarate is a prodrug of monomethyl fumarate and FDA approval was based upon clinical trials of dimethyl fumarate.
- When comparing the DMDs directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events (AEs) compared with other DMDs assessed in the eligible trials.[1]
- The newer drugs with FDA approval, cladribine and siponimod, are significantly more effective than placebo for MS, although cladribine is highlighted as having some safety concerns including a black box warning related to malignancies and teratogenicity.[1]
- For CIS, cladribine, glatiramer acetate, interferon beta-1a, interferon beta-1b, and teriflunomide significantly reduced conversion to MS compared with placebo and did not appear to be associated with more serious adverse events.[1]
- No eligible RCTs were identified to compare diroximel fumarate with placebo.[1] The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[1]
- Compared to other DMDs, the risk of infection was lower with interferon beta and glatiramer acetate.[1]

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- Overall, the risk of specific adverse events is higher with some DMDs compared to other DMDs:
    - The risk of liver injury was higher for alemtuzumab, teriflunomide, and fingolimod.[1]
    - The risk of PML was higher with fingolimod and dimethyl fumarate.[1]
- Subgroup analyses are not reported consistently across studies, but there is some evidence that women may benefit more than men with glatiramer acetate and interferon beta-1a for CIS compared to other DMDS.[1]

Recommendations:
- Revise prior authorization (PA) criteria to include newly approved DMDs (monomethyl fumarate, ozanimod, cladribine, and siponimod), add safety monitoring metrics, and renewal criteria.
- No changes to the preferred drug list (PDL) are recommended for MS therapies based on efficacy or safety data.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
Evidence for the comparative effectiveness of DMDs for management of MS was reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2017. Ocrelizumab, a new biologic approved to treat MS, was also reviewed at this meeting. Prior authorization criteria for ocrelizumab were approved by the P and T Committee to insure use in funded MS conditions. Clinical PA criteria for natalizumab were created separately from the biologic medications. In addition, PA criteria for oral multiple sclerosis drugs were amended to remove the requirement of failure of a trial of interferon beta-1a, interferon beta-1b, and glatiramer prior to approval.

At the June 2020 P and T meeting, PA changes were proposed to accommodate expanded FDA-approved indications for MS treatments until a comprehensive evidence review could be completed. Several medications for MS, which were previously approved for relapsing-remitting disease, received expanded indications in late 2019 for all forms of relapsing MS including CIS, relapsing-remitting disease, and active secondary progressive disease. In addition, PA changes were recommended to remove daclizumab from the prior authorization criteria as it was voluntarily recalled from the U.S. market due to safety concerns in 2018.

The PDL status of MS drugs is presented in **Appendix 1**. Preferred MS drugs on the PDL include: glatiramer acetate, interferon beta-1a, and interferon beta-1b. Non-preferred agents include: alemtuzumab, cladribine, dalfampridine, dimethyl fumarate, diroximel fumarate, fingolimod, ocrelizumab, ozanimod, peginterferon beta-1a, siponimod, and teriflunomide. During the first quarter of 2020, less than 10 fee-for-service (FFS) patients had claims processed for MS drugs. Most of the claims were for 2 of the non-preferred oral drugs, dimethyl fumarate (44%) and fingolimod (22%) followed by the preferred injectable agent, interferon beta-1a (33%).

Methods:
The May 2020 drug class report on DMDs for MS by 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 P and T Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

The purpose of 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.

Background:

Four distinct clinical courses have been identified for MS: CIS, RRMS, secondary progressive (SPMS), and PPMS.[2] Clinically isolated syndrome is an acute demyelinating episode lasting greater than 24 hours and is the first onset of MS symptoms. Most patients who present with CIS are eventually diagnosed with MS. Patients with RRMS have clearly defined relapses lasting 3 to 6 months with full recovery and minimal disease progression between symptomatic episodes. RRMS may be either characterized as active or not active. About 85% of patients with MS are initially diagnosed with RRMS.[3] Secondary progressive MS begins as relapsing-remitting MS, but gradual worsening of neurologic symptoms is observed over time.[4] Approximately 65% of RRMS patients will enter the secondary progressive phase.[3] Relapsing MS includes CIS, RRMS, and active SPMS in adults. Primary progressive MS is characterized by a steady decline in neurologic function and progressive accumulation of disability without acute attacks or relapses. Approximately 10-15% of MS patients have PPMS, and in contrast to RRMS, symptoms typically begin in the patients' fifth or sixth decade, a later age of onset than RRMS.[5] PPMS is distributed more equally between men and women than RRMS. The majority of available direct evidence continues to reside in patients with relapsing forms of MS rather than progressing forms of MS.

Treatment of MS falls into three main categories: symptomatic therapy to improve the patient's quality of life, treatment of acute attacks, and treatment with DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with corticosteroids and symptoms are treated accordingly with appropriate agents. DMDs are broadly categorized into 3 routes of administration: injectable, oral, and infusion therapies. Early use of DMDs in patients with RRMS has been shown to reduce the annualized relapse rate (ARR), lessen severity of relapses, and slow progression of disability.[6] Interferons have proven efficacy in managing MS and do not require substantial clinical monitoring, so they are considered first-line agents for treating MS.[6] Around 25% of patients discontinue interferon therapy within 1 to 2 years due to difficulty adhering to daily or weekly injection regimens. Patient preference and tolerance should be considered when evaluating oral versus injectable treatment options.

Ocrelizumab received FDA approval for treatment of adult patients with RRMS or PPMS in March 2017. Ocrelizumab is the only FDA-approved treatment for PPMS and provides another treatment option for RRMS patients. The efficacy of rituximab to treat PPMS has also been studied, but use is limited due to poor efficacy and serious adverse effects associated with its administration.[7] Four new oral options are available for management of MS to increase time to disability progression: monomethyl fumarate, ozanimod, siponimod and cladribine. Disease-modifying drugs that have been FDA-approved for the treatment of MS are presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage MS[8,9]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
ORAL AGENTS						
Fingolimod	GILENYA	≥ 40 kg: 0.5 mg PO once daily < 40 kg: 0.25 mg PO once daily	CIS RRMS SPMS	No	Infections, PML, bradycardia with first dose, hepatotoxicity hypertension, teratogenicity, and macular edema	Cardiac monitoring with the first dose. Ophthalmic screening at baseline and 3-4 months after

			Approved for patients ≥ 10 years of age			starting therapy. LFTs and CBC every 6 months.
Siponimod	MAYZENT	2 mg PO once daily (maintenance) 1 mg PO once daily for patients with CYP2C9*1/*3 OR *2/*3 genotype	CIS RRMS SPMS	No	Infections, bradycardia, AV conduction delays, hepatotoxicity, macular edema, hypertension, teratogenicity	CYP2C9 genotype determination before treatment initiation. CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Ozanimod	ZEPOSIA	0.92 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Teriflunomide	AUBAGIO	7 mg or 14 mg PO once daily	CIS RRMS SPMS	No	Black Box Warnings: Hepatotoxicity and Teratogenicity Other Warnings: infections and hypertension	CBC, LFTs, and blood pressure every 6 months
Dimethyl Fumarate	TECFIDERA	240 mg PO twice a day (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Monomethyl Fumarate	BAFIERTAM	190 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Diroximel Fumarate	VUMERITY	462 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Cladribine	MAVENCLAD	Cumulative dose of 3.5 mg/kg PO divided into 2 yearly treatment courses (1.75 mg/kg per treatment course).	RRMS SPMS	No	Black Box Warnings: Malignancies and Teratogenicity Other Warnings: Bone marrow suppression, PML, lymphopenia, infections, cardiac failure, and hepatoxicity **Due to its safety profile, cladribine is recommended for patients who have had an inadequate response to, or*	CBC with lymphocyte count and LFTs every 6 months

					*who are unable to tolerate an alternative MS treatment**	
INJECTABLE AGENTS						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years and cumulative dose of 140 mg/m^2	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity **Considered as last resort treatment for patients that have failed other therapies**	ECG and LVEF before each infusion. CBC and LFTs every 6 months
Glatiramer Acetate	COPAXONE, GLATOPA	20 mg SC once daily; OR 40 mg SC three times a week	CIS RRMS SPMS	No	Transient post injection reactions (chest pain, dyspnea, tachycardia, anxiety, palpitations, flushing, urticaria)	None required
Interferons						
Interferon beta-1a	AVONEX	30 mcg IM once weekly (maintenance)	CIS RRMS SPMS	No	Hepatotoxicity, thrombocytopenia, increased risk of spontaneous abortion, depression, and suicidal ideation	CBC and LFTs every 6 months
Interferon beta-1a	REBIF	22 or 44 mcg SC three times a week				
Interferon beta-1b	BETASERON, EXTAVIA	250 mcg SC every other day				
Peginterferon beta-1a	PLEGRIDY	125 mcg SC every 14 days				
Monoclonal Antibodies						
Alemtuzumab	LEMTRADA	Intravenous infusion for 2 or more treatment courses. First course: 12 mg IV over 4 hours once a day for 5 consecutive days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS SPMS	Yes	Black Box Warnings: Autoimmunity, Infusion Reactions, Stroke, and Malignancies Other Warnings: infections, PML, thyroid autoimmunity, glomerular nephropathies, thrombocytopenia, autoimmune hepatitis **Due to safety profile, reserve for patients who have inadequate response to 2 or more MS drugs**	Thyroid function every 3 months. CBC with differential, serum creatinine, and urinalysis every month. Baseline and yearly LFTs and skin exams.
Natalizumab	TYSABRI	300 mg via IV infusion every 4 weeks	CIS RRMS SPMS	Yes	Black Box Warnings: PML Other Warnings: infections, hypersensitivity, teratogenicity, thrombocytopenia, hepatotoxicity **consider risk of PML vs. benefit of therapy**	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months

Ocrelizumab	OCREVUS	600mg IV every 6 months (maintenance)	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy
Abbreviations: AML = acute myeloid leukemia; CBC = complete blood count; CIS = clinically isolated syndrome; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; IM = Intramuscular; IV = Intravenous; JCV = John Cunningham virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; MS = multiple sclerosis; MRI = magnetic resonance imaging; PO = Oral; PPMS = primary progressive multiple sclerosis; PML = progressive multifocal leukoencephalopathy; REMS = Restricted Evaluation and Mitigation Strategy; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous, SPMS = secondary progressive multiple sclerosis						

Progression of MS is assessed by the amount of disability caused by the disease. The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS. The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), with lower scores indicating more mobility and activity by the patient.[10] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[11] In addition, it is nonlinear over its range in comparison with the actual level of function and it places a much greater emphasis on ambulation status than other neurologic functions.[10] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression when assessed over 3 to 6 months as an increase in EDSS of 0.5 points when the score is between 5.6 to 8.5 and 1.0 point when the score is between 0 and 5.5.[12] Some researchers have proposed that longer trials (with duration of at least 1 year) with greater changes in the EDSS scores (greater than 1-2 points) may better identify patients with sustained disability.[13] Because of the limitations of the EDSS, the National MS Society task force developed the Multiple Sclerosis Functional Composite (MSFC) score. This score is a composite measure of walking speed, upper-limb movements, and cognition. There is no defined range for the MSFC score; negative values indicate worsening and positive values indicate improvement. Similar to the EDSS, researchers have had difficulty quantifying a meaningful change in MSFC scores. Individual components of the test may change over time which may not be reflected in composite scores.[12]

The ARR is often included as an outcome measure for MS clinical trials because it is easy to quantify. Relapses are generally defined as neurologic symptoms lasting more than 24 hours which occur at least 30 days after the onset of a preceding event.[12] However, the probability of relapse is not a consistent function over time. Patients are usually enrolled in a trial at the time of MS diagnosis when the probability for relapses is high, and as time progresses, this probability decreases due to the regression to the mean phenomenon.[12] In order to have enough power to detect a significant reduction in relapses, research suggests a clinical trial needs to last at least 1 year, but this measure may also be less meaningful than evaluating the total number of relapses over a longer period of time.[14] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[14] MRI lesion counts may assist clinicians in tool to assess disease progression. However, there is a poor correlation between MRI activity, a surrogate endpoint for CNS disease, and relapse rate as the appearance of new MRI lesions often outnumber clinical relapses.[14] This paradox in MS became apparent when MRI was first used in MS and attempts to correlate T2 lesions with EDSS revealed a dissociation between the two measures.[15]

DERP Summary Findings:

The 2020 DERP drug class review on DMDs for MS was the fourth update of the original 2007 report. The DERP authors searched Ovid MEDLINE and the Cochrane Library from January 1, 2016 up to October 15, 2019, and several other websites to identify eligible studies.[1] For new drugs not included in the previous DERP reports, the authors searched from database inception.[1] The Ovid MEDLINE search was rerun on February 3, 2020 to capture any studies published since the initial search in October 2019. Fourteen new RCTs were identified for the 2020 update.[1] Overall, the DERP MS summary includes 42 RCTs and 30 observational studies. All the RCTs were assessed as being fair- or poor-quality using the GRADE methodology.[1] DERP used the following health outcomes to assess efficacy: disability, clinical exacerbation/relapse, quality of life, functional outcomes (wheelchair use, time lost from work), and persistence (drug

discontinuation rates). Harms associated with drug therapy were assessed using the incidence of overall AEs, serious AEs, withdrawals due to AEs, and specific AEs such as hepatoxicity.

1. Effectiveness and Harms of DMDs for MS

A. When compared directly, the following therapies were significantly more effective in reducing relapses than the active comparator.[1]

Alemtuzumab vs. Interferon Beta-1a 44 mcg (Meta-Analysis of 3 RCTs; 1472 participants)

Three RCTs compared alemtuzumab 12 mg infusion with interferon beta-1a 44 mcg subcutaneous (SC) injection over 24 to 36 months in adults with RRMS.[1] The fair-quality trials had some risk of bias due to lack of blinding, high loss to follow-up, author conflicts of interest, and funding by industry.[1] The following data is derived from a meta-analysis of the 3 RCTs, unless stated otherwise. Compared to interferon beta-1a, alemtuzumab significantly reduced the proportion of relapses at 24 months (risk ratio [RR] 0.65; 95% CI, 0.48 to 0.88) and at 36 months (RR 0.52; 95% CI, 0.34 to 0.80; moderate quality of evidence [QoE]).[1] Alemtuzumab significantly reduced the proportion of disability progression at 24 months (RR 0.73; 95% CI, 0.54 to 0.99) and at 36 months (RR 0.33; 95% CI, 0.15 to 0.70; low QoE).[1] Alemtuzumab improved disability, as measured by the EDSS, at 36 months (mean difference [MD] -0.07; 95% CI, -1.04 to -0.36), but not at 24 months (MD -0.20; 95% CI, -0.60 to 0.20; low QoE).[1] However, the changes in EDSS were small and are unlikely to be clinically meaningful.[1] Alemtuzumab improved function compared to interferon, as measured by the MSFC at 24 months, but the clinical importance of the improvement is not clear as the MSFC changes were small (MD 0.10; 95% CI, 0.05 to 0.16; meta-analysis 2 RCTs; moderate QoE).[1] Participants in the alemtuzumab groups had higher levels of study completion compared to interferon beta-1a at 36 months (RR 1.37; 95% CI, 1.15 to 1.63), but not at 24 months (RR 1.16; 95% CI, 0.98 to 1.37; low QoE).[1]

The 3 RCTs reported the same AEs with both medications. For alemtuzumab, patients reported headache (43% to 61%), nausea (14% to 24%), rash (39% to 91%), and fever related to the infusion (16% to 37%).[1] In the alemtuzumab group, patients also reported nasopharyngitis (20% to 29%), urinary tract infections (11% to 21%), herpes viral infections (8% to 16%), and upper respiratory tract infections (15% to 59%).[1] In the interferon beta-1a group, patients reported influenza-like illness (8% to 27%), injection-site erythema (25%), headache (19% to 63%), and relapse (33% to 39%).[1] No significant differences in serious AEs at 24 months or 36 months were reported between the 2 medications (very low QoE).[1]

Fingolimod vs. Interferon Beta-1b 250 mcg (1 RCT; 157 participants)

One poor-quality RCT conducted over 18 months compared oral fingolimod with SC interferon beta-1b 250 mcg in adults with RRMS.[1] Lack of reporting of key trial components (including randomization), high losses to follow-up, and author conflicts of interest contributed to the high risk of bias for this trial.[1] The authors designed the trial to provide evidence for the effect of fingolimod and interferon beta-1b on cognitive, MRI and clinical outcomes.[1] A direct comparison between fingolimod and interferon beta-1b was not a prespecified objective. Fingolimod reduced relapse rates numerically compared to interferon beta-1b, but the statistical significance is not clear (ARR 0.12 vs. 0.39; P value between groups not reported; low QoE).[1] No significant difference in disability as measured by the EDSS was observed (mean increase of 0.12 fingolimod vs. 0.19 interferon; P value not reported; low QoE).[1] Disability progression and changes in function (MSFC) were not evaluated. Overall, significantly more participants randomized to fingolimod completed the 18-month trial compared with those randomized to interferon beta-1b (91.5% vs. 58.8%; RR 1.56; 95% CI, 1.23 to 1.97; P <0.001; moderate QoE).[1]

Overall, patients in the fingolimod groups reported more adverse events than patients in the interferon beta-1b group (79.81% vs. 59.57%; P=0.009; low QoE).[1] The most commonly reported adverse events in the fingolimod group were infections and infestations (28%, primarily nasopharyngitis and influenza) and changes in liver function tests (25%, primarily alanine aminotransferase, cholesterol and transaminase increases).[1] In the interferon beta-1b group, the most

commonly reported adverse events were nervous system disorders (26%, primarily MS relapses) or general disorders and administration-site conditions (21%, primarily fever, fatigue and influenza-like illnesses).[1] No significant difference in serious AEs was noted between fingolimod and interferon beta-1b (8.65% vs. 2.13%; P=0.14; low QoE).[1]

Fingolimod vs. Interferon Beta-1a 30 mcg (1 RCT; 1292 participants)

One fair-quality RCT conducted over 12 months compared oral fingolimod 0.5 mg and 1.25 mg with intramuscular (IM) interferon beta-1a 30 mcg in adults with RRMS.[1] Concerns about the potential for unblinding because of adverse events, author conflicts of interest, and funding by industry downgraded the quality assessment of this RCT.[1] Fingolimod significantly reduced relapse rates compared to interferon beta-1a (ARR 0.16 vs. 0.33; P<0.001; low QoE).[1] At 12 months, levels of disability for patients in the fingolimod and in the interferon beta-1a group remained relatively stable, and there was no significant difference between the groups (p=0.06; low QoE).[1] No significant differences in disability progression, function as measured by the MSFC, or disability as measured by the EDSS were noted at 12 months (low QoE).[1] No difference between fingolimod and interferon beta-1a was observed in study persistence (moderate QoE). No significant differences in serious AEs related to increased liver enzymes, macular edema or infections were associated with either drug (low QoE).[1]

Ocrelizumab vs. Interferon Beta-1a (3 RCTs; 1876 participants)

Three RCTs compared ocrelizumab infusion and IM or SC interferon beta-1a over 6 to 24 months in adults with RRMS.[1] The smaller trial (n=220) was assessed as poor-quality due to concerns about lack of blinding, the shorter length of follow-up, author conflict of interests, and funding by industry.[1] The two larger, 24-month trials (n=821 and n=835) are fair-quality; however, some risk of bias was identified due to author conflict of interests and funding by industry.[1] Ocrelizumab significantly reduced relapse rates compared to interferon beta-1a (ARR 0.13 vs. 0.36; P=0.03 and ARR 0.16 vs. 0.29; P<0.001; 1 RCT and pooled analysis of 2 RCTs; n=1876; low QoE).[1] Ocrelizumab significantly reduced disability progression compared to interferon beta-1a (hazard ratio [HR] 0.60; 95% CI, 0.45 to 0.81; pooled analysis of 2 RCTs; n=1656; low QoE;).[1] Compared to interferon beta-1a, ocrelizumab improved functioning (MD 0.07; 95% CI, 0.02 to 0.13), as measured by the MSFC, but the clinical importance of the small difference is not clear (meta-analysis of 2 RCTs; n=1656; moderate QoE:).[1] Change in disability (EDSS) was not evaluated. Ocrelizumab significantly increased persistence compared to interferon beta-1a at 24 months (RR 1.10; 95% CI, 1.05 to 1.15; meta-analysis 3 RCTs; n=1656; low QoE), but not at 6 months (1 RCT; n=220; low QoE).[1] No significant difference in serious AEs was observed between ocrelizumab and interferon beta-1a (RR 0.79; 95% CI, 0.56 to 1.09; meta-analysis of 3 RCTs; n=1876; low QoE).[1]

Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 mcg (2 RCTs; 2666 participants)

Two fair-quality RCTs compared oral ozanimod 0.5 mg and 1 mg once daily with IM interferon beta-1a 30 mcg once weekly over 12 to 24 months in adults with relapsing MS.[1] Risk of bias included concerns about author conflict of interests and funding by industry.[1] Ozanimod significantly reduced relapse rates (ARR 0.24, ozanimod 0.5 mg; ARR 0.18, ozanimod 1 mg) compared to interferon beta-1a (ARR 0.35) for at least 12 months (rate ratio, ozanimod 0.5 mg vs. interferon beta-1a, 0.69; 95% CI, 0.55 to 0.86; rate ratio, ozanimod 1 mg vs. interferon beta-1a, 0.52; 95% CI, 0.41 to 0.66; 2 RCTs; low QoE).[1] No significant difference between each of the 3 treatment groups was observed in disability rate progression at 24 months (9.3% ozanimod 0.5 mg, vs. 12.5% vs. ozanimod 1 mg, vs. 11.3% interferon beta-1a; P>0.05; 2 RCTs; low QoE).[1] Over 24 months ozanimod 0.5 mg significantly improved function as measured by the MSFC compared to interferon beta-1a (MD 0.10; 95% CI, 0.01 to 0.19), but no difference was noted with ozanimod 1 mg (MD 0.06; 95% CI, -0.03 to 0.15; 1 RCT; n=1320; very low QoE).[1] However, the clinical importance of the nominal difference is not clear.[1] Change in disability (EDSS) was not evaluated. No significant difference in persistence was observed at 24 months (RR 1.03; 95% CI, 0.97 to 1.08; 1 RCTs; n=1320; very low QoE).[1]

The most frequently reported adverse events in the ozanimod groups were nasopharyngitis (13% to 16%), alanine aminotransferase increases (6% to 7%), hypertension (5% to 6%), γ-glutamyltransferase increase (4% to 6%), pharyngitis (4% to 6%), and urinary tract infection in the ozanimod groups (4% to 5%).[1] The

most frequent adverse events in the interferon beta-1a group were influenza-like illness (incidence not reported), headache (incidence not reported), nasopharyngitis (11%), upper respiratory tract infection (incidence not reported), fever (incidence not reported), and orthostatic hypotension (incidence not reported).[1] No significant difference in serious AEs was noted at 24 months (RR 1.06; 95% CI, 0.69 to 1.64; 1 RCT; n=1320; very low QoE).[1]

Teriflunomide 7 mg and 14 mg vs. Interferon Beta-1a (1 RCT; 324 participants)

One fair-quality RCT compared oral teriflunomide 7 mg and 14 mg once daily with SC interferon beta-1a 44 mcg three times a week for up to 12 months in adults with relapsing MS.[1] Risk of bias included concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.[1] Teriflunomide 7 mg significantly reduced relapse rates compared to interferon beta-1a (ARR 0.41 vs. 0.22; P=0.03), but no significant differences were observed with teriflunomide 14 mg (RR 0.26 vs. 0.22; P=0.59; low QoE).[1] Disability progression, changes in disability (EDSS), and changes in function (MSFC) were not evaluated. Teriflunomide 7 mg significantly increased persistence (RR 1.20; 95% CI, 1.02 to 1.40), but the difference was only marginal with teriflunomide 14 mg (RR 1.17; 95% CI, 1.00 to 1.38; very low QoE).[1]

Patients in the 2 teriflunomide groups reported higher rates of nasopharyngitis than did patients in the interferon beta-1a group (20% to 26% vs. 18%), as well as higher rates of diarrhea (21% to 23% vs. 8%), hair thinning (6% to 20% vs. 1%), paresthesia (10% to 13% vs. 8.0%), and back pain (10% vs. 8%).[1] Patients in the interferon beta-1a group reported influenza-like symptoms (54% vs. 3% to 4%), alanine aminotransferase increases (31% vs. 10% to 11%), and headache (26% vs. 16% to 21%) more frequently than patients in the teriflunomide groups.[1] Teriflunomide 7 mg increased the number of serious AEs compared to placebo, but the difference was not significant (RR 1.57; 95% CI, 0.64 to 3.84), and no significant differences were noted between placebo and teriflunomide 14 mg (very low QoE).[1]

Cladribine in combination with Interferon Beta (various formulations) vs. Interferon Beta (various formulations) Monotherapy (1 RCT; 172 participants)

One poor-quality RCT compared cladribine (3.5 mg/kg) plus existing of interferon-beta therapy to existing interferon-beta therapy plus a placebo in adults with relapsing MS over a 24-month study period.[1] The trial was designed to evaluate a 5.25 mg/kg dosage of cladribine, but was discontinued because of an association with lymphopenia.[1] Risk of bias included concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.[1] Cladribine plus interferon beta significantly reduced relapse rate compared to interferon beta alone (ARR 0.12 vs. 0.32; RR 0.37; 95% CI, 0.22 to 0.63; moderate QoE).[1] No significant difference in disability progression was observed (15.3% vs. 12.5%; P value not reported; low QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated. Overall, 64.5% (80 of 124) of participants in the combination therapy group completed the 96-week trial compared with 81.3% (39 of 48) of participants in the interferon beta group, with persistence being significantly lower in the combination therapy (P value not reported; low QoE).[1]

The most commonly reported adverse events in the cladribine plus interferon beta group were lymphopenia (40%), headache (25%), and nasopharyngitis (23%).[1] In the placebo plus interferon beta group, patients commonly reported headache (21%), nasopharyngitis (17%), and upper respiratory tract infection (17%).[1] In the cladribine plus interferon beta group, 3.2% of participants had serious infections or infestations, compared with no participants in the placebo plus interferon beta group.[1] Participants in the cladribine plus interferon beta group also had higher rates of neoplasms, including 1 report of squamous cell carcinoma, than participants in the placebo plus interferon beta group (4.0% vs. 0%).[1] Elevated levels of alanine transaminase and aspartate transaminase were seen in 2 participants in the cladribine plus interferon beta group and 1 patient in the placebo plus interferon beta group (1.6% vs. 2.1%).[1] No significant difference in serious AEs was observed between treatment groups (P value not reported; low QoE).[1]

Glatiramer Acetate in combination with Interferon Beta-1a vs. Interferon Beta-1a Monotherapy (1 RCT; 1008 participants)

One fair-quality RCT compared the combination of SC glatiramer acetate and IM interferon beta-1a versus interferon beta-1a monotherapy over 36 months in adults with RRMS.[1] Concerns about high loss to follow-up and author conflicts of interest contributed to the fair-quality assessment of this RCT.[1] Glatiramer acetate plus interferon beta-1a reduced relapse rates compared with interferon beta-1a alone (ARR, 0.12 vs. 0.16; P=0.02; 95% CI not reported; low QoE).[1] No significant difference in disability progression was observed between the combination therapy and monotherapy (23.9% vs. 21.6%; P>0.05; low QoE).[1] Patients experienced similar improvements in function (MSFC) in the 2 treatment groups (0.1 interferon beta-1a vs. 0.1 combination; P>0.05; low QoE).[1] Change in disability (EDSS) was not evaluated. The completion rates at 36 months for each treatment group were similar in the combination group (79.6%) and in the interferon beta-1a group (77.6%; low QoE).[1] No significant difference in serious AEs was observed with interferon beta-1a alone or glatiramer acetate in combination with interferon beta-1a (low QoE).[1]

B. When compared directly, the following therapies were not significantly different for relapse.[1]

Dimethyl Fumarate vs. Glatiramer Acetate (1 RCT; 1430 participants)

One poor-quality RCT compared oral dimethyl fumarate with SC glatiramer acetate over 24 months in adults with RRMS.[1] Concerns about author conflicts of interest, funding by industry, and the potential for unblinding in the dimethyl fumarate groups (a flushing reaction is known to be an adverse effect associated with dimethyl fumarate) resulted in downgrading the quality assessment of this RCT.[1] Different doses of dimethyl fumarate were compared to placebo. The RCT was not designed to test the superiority or noninferiority of dimethyl fumarate compared with glatiramer acetate.[1] A post hoc evaluation was conducted to provide direct comparison of dimethyl fumarate with glatiramer acetate.[1] The statistical testing for this direct comparison should be considered exploratory, and not definitive.[1] No significant difference in disability progression between dimethyl fumarate and glatiramer acetate was observed (HR 0.85; 95% CI, 0.56 to 1.29 very low QoE).[1] No significant difference in disability was seen for dimethyl fumarate compared with glatiramer acetate (P=0.37; very low QoE).[1] In the direct post hoc comparison, participants in the dimethyl fumarate and glatiramer acetate groups had similar ARRs at 2 years (rate ratio, 0.78; 95% CI, 0.59 to 1.05; very low QoE).[1] When compared directly, similar number of participants in the dimethyl fumarate and glatiramer acetate groups relapsed at 2 years (HR, 0.92; 95% CI, 0.70 to 1.22; very low QoE).[1] No significant difference between dimethyl fumarate and glatiramer acetate was observed in study persistence (no P value reported; moderate QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] No significant differences in serious AEs were noted between dimethyl fumarate and glatiramer acetate (no P value reported; low QoE).[1]

Glatiramer Acetate vs. Interferon Beta-1b 250 mcg (2 RCTs; 2319 participants)

Two RCTs compared SC glatiramer acetate 20 mg with SC interferon beta-1b 250 mcg over 2 to 3.5 years in adults with RRMS and CIS.[1] The smaller trial (n=75) conducted over 2 years, was rated as poor quality due to the lack of blinding, small sample size, author conflict of interests, and funding by industry.[1] The second, longer duration trial (n=2244) was of fair quality, but risks of bias were identified due to the method of analysis (per-protocol), author conflict of interests, and funding by industry.[1] No significant difference in relapse rates between glatiramer acetate and interferon beta-1b was noted (2 RCTs; low QoE).[1] No significant difference in disability progression was observed between glatiramer acetate and interferon beta-1b (20% vs. 21%; P=0.68; 1 RCT; low QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated. No significant difference in persistence was observed (meta-analysis of 2 RCTs; moderate QoE).[1] No significant difference in serious AEs was observed (P value not reported; 1 RCT; low QoE).[1]

Glatiramer Acetate vs. Interferon Beta-1a 30 mcg or 44 mcg (3 RCTs; 1937 participants)

Three RCTs compared glatiramer acetate and interferon beta-1a over 24 to 36 months in adults with RRMS.[1] One trial (n=1008) was assessed as fair-quality due to concerns about high loss to follow-up and author conflicts of interest.[1] The other 2 trials (n=165 and n=764) were of poor methodological quality because of

concerns about randomization and blinding, high loss to follow-up, author conflicts of interest, and funding by industry.[1] No significant difference in relapse rates between glatiramer acetate and interferon beta-1a at 24 or 36 months were observed, although the proportion was numerically lower with glatiramer acetate at 36 months (20% vs. 26%; 2 RCTs; n=1772; low QoE).[1] No significant difference in disability progression was observed between either drug (2 RCTs; n=1772; very low QoE).[1] Glatiramer acetate significantly increased persistence at 24 months (RR, 1.08; 95% CI, 1.02 to 1.15) and at 36 months (RR, 1.08; 95% CI, 1.01 to 1.16; meta-analysis of 3 RCTs; n=1687; low QoE).[1] No significant difference in disability as measured by the EDSS was noted (1 RCT; n=165; low QoE).[1] No significant difference in function as measured by the MSFC was reported (1 RCT; n=1008; Low QoE).[1] No significant difference in serious AEs between glatiramer acetate and interferon beta-1a was observed (RR 0.84; 95% CI, 0.60 to 1.17; meta-analysis of 2 RCTs; n=1772; very low QoE).[1]

Interferon Beta-1b 250 mcg vs. Interferon Beta-1a 30 mcg and 44 mcg (4 RCTs; 648 participants)

Four fair- to low-quality RCTs compared interferon beta-1b and interferon beta-1a over 12 to 24 months in adults with RRMS and CIS. Risks of bias included lack of blinding, method of analysis (per-protocol rather than intention-to-treat), no randomization details, and lack of reporting of author conflicts of interest.[1] No significant difference in relapse was observed between interferon beta-1b and interferon beta-1a at 24 months (RR 0.85; 95% CI, 0.59 to 1.21; meta-analysis of 4 RCTs; n=648; very low QoE).[1] No significant difference in disability progression was noted between interferons at 24 months (RR 0.63; 95% CI, 0.34 to 1.16; meta-analysis of 2 RCTs; n=489; very low QoE).[1] There was no significant difference in disability, as measured by the EDSS, at 12 or 24 months (meta-analysis of 4 RCTs; n=648; very low QoE).[1] No significant difference in persistence was noted at 24 months (meta-analysis of 4 RCTs; n=648; very low QoE).[1] Serious AEs were not evaluated.

C. When compared with placebo, the following therapies were significantly more effective in reducing relapse.[1]

Cladribine vs. Placebo (1 RCT; 1326 participants)

One fair-quality RCT compared oral cladribine and placebo over 24 months in adults with RRMS.[1] Participants were randomized to 3.5 mg/kg of cladribine, 5.25 mg/kg of cladribine, or placebo. Concerns about baseline differences between treatment groups and funding by industry downgraded the quality assessment of this trial.[1] The FDA-approved cladribine dosage is a cumulative dose of 3.5 mg/kg. Cladribine is only indicated for the treatment of adults with RRMS and active SPMS. Cladribine is serious safety concerns and the manufacturer's label contains a black box warning related to malignancies and teratogenicity. Because of its adverse effect profile, cladribine is generally reserved for patients who do not tolerate or have inadequate response to other drugs for MS. Compared to placebo, cladribine 3.5 mg/kg significantly reduced relapse rates over 24 months (ARR 0.33 vs. 0.14; P<0.001; low QoE).[1] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[1] Cladribine 3.5 mg/kg significantly reduced disability progression compared to placebo (HR 0.67; 95% CI, 0.48 to 0.93; low QoE).[1] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] Persistence was significantly higher in the cladribine 3.5 mg/kg group compared with placebo (91.9% vs. 87%; P value not reported; low QoE).[1] In the non-FDA approved dose group, 89.0% of participants in the 5.25 mg/kg completed the study.[1]

The most common adverse events reported by participants were headache (17% to 24%), lymphocytopenia (22% to 32% in the cladribine groups, vs. 2% in the placebo group), nasopharyngitis (13% to 14%), upper respiratory tract infection (10% to 13%), and nausea (9% to 11%).[1] In addition, 2.3% of participants in the cladribine 3.5 mg/kg group reported infections and infestations compared to 1.6% of those on placebo.[1] Neoplasms (benign, malignant, and unspecified) were diagnosed in 1.4% of participants in the cladribine 3.5 mg/kg group.[1] No neoplasms were reported in the placebo group.[1] There were 3 cases of cancer in the cladribine 3.5 mg/kg group (1 melanoma, 1 pancreatic cancer, and 1 ovarian cancer).[1] In addition, 20 patients in the cladribine groups (8 patients at 3.5 mg/kg vs. 12 patients at 5.25 mg/kg) developed herpes zoster infections.[1] No significant difference in serious AEs between cladribine and placebo were reported (P value note reported; low QoE).[1]

Peginterferon beta-1a vs. Placebo (1 RCT; 1012 participants)

One fair-quality RCT compared SC peginterferon beta-1a 125 mcg every 2 weeks with placebo over 48 weeks in adults with RRMS.[1] Concerns about differential loss to follow-up, author conflicts of interest, and funding by industry contributed to the fair-quality assessment of this trial.[1] Peginterferon beta-1a significantly reduced relapse rates compared to placebo (ARR 0.26 vs. 0.40; rate ratio 0.64; 95% CI, 0.50 to 0.83; low QoE).[1] Compared to placebo, peginterferon beta-1a significantly reduced disability progression (HR 0.62; 95% CI, 0.40 to 0.97; moderate QoE).[1] Changes in disability (EDSS) and function (MSFC) were not evaluated.[1] Overall, 85.5% of participants in the peginterferon beta-1a group completed the 48-week trial compared with 91.2% of participants in the placebo group, with lower persistence in the peginterferon group (P value not reported; moderate QoE).[1] No significant difference in serious AEs between peginterferon beta-1a and placebo was reported (low QoE).[1]

Siponimod vs. Placebo (2 RCTs; 1756 participants)

Two fair-quality RCTs that compared siponimod to placebo were identified for inclusion in the DERP report.[1] Concerns about author conflict of interest and funding by industry were the 2 issues that impacted quality assessment for these RCTs.[1] In the larger trial, 1651 adults with SPMS were randomized to oral siponimod 2 mg once daily or placebo for up to 3 years.[1] In the smaller trial, 188 adults with RRMS were randomized to 1 of 4 groups; siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo once daily for 6 months.[1] The FDA-recommended maintenance dose for siponimod is 2 mg for adults with relapsing MS and 1 mg for adults with a CYP2C9*1/*3 or *2/*3 genotype.[1] Siponimod 2 mg significantly reduced relapse in RRMS (ARR ratio 0.45; 95% CI, 0.34 to 0.59) and in SPMS (ARR 0.20 vs. 0.58; P=0.04; 2 RCTs; moderate QoE) compared to placebo.[1] Siponimod 2 mg significantly reduced disability progression in adults with SPMS (HR 0.79; 95% CI, 0.65 to 0.95; 1 RCT; low QoE;).[1] No significant difference in function was observed between siponimod 2 mg and placebo, as measured by the MSFC in patients with SPMS (p=0.08; 1 RCT; very low QoE).[1] In the larger trial, 81.7% of participants with SPMS in the siponimod 2 mg group completed the trial compared with 77.7% in the placebo group, with a maximum trial duration of 3.5 years (P=0.06; low QoE).[1] Change in disability (EDSS) was not evaluated.

In the siponimod 2 mg groups, the most commonly reported adverse events were headache (31%), nasopharyngitis (12%), vertigo (12%), infections and infestations (49%), and hypertension (12%).[1] In the placebo groups, the most commonly reported adverse events were infections and infestations (49%), dizziness (9% to 13%), nasopharyngitis (11% to 19%), and upper respiratory tract infections (0% to 16%).[1] Serious adverse events in the siponimod groups included second-degree atrioventricular block (6%), intentional overdose (2%), and urinary tract infection (1%).[1] Serious adverse events in the placebo groups included urinary tract infection (1%), suicide attempt (1%), gait disturbance (1%), and paraparesis (i.e., partial paralysis of the legs; 1%).[1] Overall, 2 patients (1 in the siponimod group and 1 in the placebo group) were diagnosed with a basal cell carcinoma.[1] Participants in the siponimod groups and in the placebo groups had raised alanine aminotransferase levels (1% vs. <1% in SPMS; 8% vs. 0 in RRMS) and raised aspartate aminotransferase levels (<1% vs. <1% in RRMS; results in SPMS patients not reported).[1] No significant differences in serious AEs were identified between siponimod 2 mg and placebo in patients with SPMS or RRMS (RR 11.16; 95% CI 0.62 to 202.40 in adults with RRMS and RR 1.18; 95% CI 0.93 to 1.49 in adults with SPMS; 2 RCTs; very low QoE).[1]

Ozanimod 0.5 mg and 1 mg vs. Placebo (1 RCT; 258 participants)

One poor-quality, phase 2 RCT compared ozanimod 0.5 mg or 1 mg with placebo in adults with relapsing MS over 24 weeks.[1] Risk of bias included concerns about baseline differences, short duration of follow-up, author conflict of interest, and funding by industry.[1] No significant difference in relapse rates with ozanimod compared to placebo was reported (ARR 0.35 0.5 mg, vs. 0.50 placebo; OR, 0.69; 95% CI, 0.36 to 1.34; ARR 0.24 1 mg, vs. 0.50 placebo; OR, 0.47; 95% CI, 0.22 to 1.01; low QoE).[1] Participants in both ozanimod groups were more likely to be relapse-free at 24 weeks than participants in the placebo group, but this difference was not formally statistically tested (83% ozanimod 0.5 mg, vs. 89% ozanimod 1 mg, vs. 77% placebo; *P* value not reported).[1] No significant difference

in persistence between groups was observed (97.7% ozanimod 0.5 mg; 98.8% ozanimod 1 mg; 96.6% placebo; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated.

The most commonly reported adverse events in the ozanimod groups were nasopharyngitis (6% to 13%), headache (4% to 6%), and urinary tract infection (2% to 7%).[1] Participants in the placebo groups also experienced these adverse events, with the proportions of headache (9%) and nasopharyngitis (14%) numerically higher in the placebo group compared with the ozanimod groups.[1] In the ozanimod 0.5 mg group, 3 serious treatment-emergent adverse events occurred (3%) and were assessed as being unrelated to treatment (optic neuritis, somatoform autonomic dysfunction, and uterine cervical squamous metaplasia).[1] Increased alanine aminotransferase greater than 3 times the upper limit of normal occurred in 3 participants in the ozanimod groups.[1] No significant difference in serious AEs was noted (very low QoE).[1]

Diroximel Fumarate vs. Placebo

No eligible studies were identified to compare diroximel fumarate with placebo. The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[1] Since FDA-approval, 1 ongoing study and 1 published RCT evaluating the efficacy and safety of diroximel fumarate were published; however, neither study met DERP inclusion criteria for this report.[1]

2. Effectiveness and Harms of DMDs for CIS

Cladribine vs. Placebo (1 RCT; 412 participants)

One poor-quality RCT compared cladribine 3.5 mg/kg and placebo over 24 months in adults with a first clinical demyelinating event.[1] Risks of bias included high and differential loss to follow-up, early termination, author conflict of interest, and funding by industry.[1] This trial was terminated early because the sponsor suspended the development of cladribine. Cladribine is not FDA-approved for use in people with CIS because of concerns about safety.[1] Cladribine significantly reduced conversion to MS compared to placebo (HR 33; 95% CI, 0.21 to 0.51; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. Compared to placebo, cladribine significantly reduced persistence (RR 0.90; 95% CI, 0.82 to 0.99; low QoE).[1]

The most commonly reported adverse events in the cladribine and placebo groups were headache (31% vs. 28%) and nasopharyngitis (17% vs. 18%).[1] Participants in the cladribine group contracted herpes virus infections at a higher rate than participants in the placebo group (8% vs. 1%).[1] Overall, 3 patients in the cladribine group and 6 patients in the placebo group were diagnosed with neoplasms.[1] Of these, 2 patients in the cladribine 3.5 mg/kg group were diagnosed with cancer; 1 with papillary thyroid cancer and 1 with squamous cell carcinoma.[1] No significant difference between cladribine and placebo in serious adverse events was observed (11% vs. 10%; p value not reported; low QoE).[1]

Glatiramer Acetate 20 mg vs. Placebo (1 RCT; 481 participants)

One fair-quality RCT compared SC glatiramer acetate to placebo over 36 months in people with CIS.[1] Concerns about early termination of the study due to benefit observed with glatiramer, author conflict of interest, and funding by industry contributed to the quality assessment of this RCT.[1] Compared to placebo, glatiramer acetate reduced conversion to MS (HR, 0.55; 95% CI, 0.40 to 0.77; moderate QoE).[1] Patients in the glatiramer acetate group also had a lower risk of a second attack (24.7% vs. 42.9%; OR 0.41; 95% CI, 0.28 to 0.62).[1] The time to conversion to MS was also longer in the glatiramer acetate group compared with the placebo group (722 days vs. 336 days; P=0.004).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. No

significant difference in persistence between glatiramer acetate and placebo was noted (84.8% vs. 91.2%; p value not reported; low QoE).[1] No significant difference in serious adverse events was observed (8% glatiramer acetate vs. 5% placebo; P value not reported; low QoE).[1]

Interferon Beta-1b 250 mcg vs. Placebo (1 RCT; 487 participants)

One fair-quality RCT compared SC interferon beta-1b with placebo over 24 months in adults with a first clinical demyelinating event.[1] Risks of bias included concerns about author conflict of interest and funding by industry.[1] Compared to placebo, interferon beta-1b significantly reduced conversion to MS (HR 0.50; 95% CI, 0.36 to 0.70; moderate QoE).[1] Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated. No significant difference in persistence was noted between the interferon (78.7%) and placebo groups (84.6%; p value not reported; low QoE).[1] No significant difference in serious adverse events between groups was observed (very low QoE).[1]

Interferon Beta-1a (various doses) vs. Placebo (4 RCTs; 1411 participants)

Four RCTS compared interferon beta-1a SC and IM dosing regimens with placebo over 2 to 3 years in adults with a first episode suggestive of MS, including a first clinical demyelinating event.[1] Three trials were assessed as fair-quality due concerns about lack of reporting on randomization, author conflict of interest, and funding by industry.[1] One trial (n=217) was evaluated as poor-quality due to lack of reporting on key study components (including randomization and blinding), intent-to-treat analysis not being conducted, and no information on author conflicts of interest or study funding.[1] Compared to placebo, interferon beta-1a significantly reduced conversion to MS at 2 years (RR 0.80; 95% CI, 0.68 to 0.95) and at 3 years (RR 0.62; 95% CI, 0.50 to 0.78; meta-analysis of 4 RCTs; low QoE).[1] No significant difference in disability, as measured by the EDSS was reported (1 RCT; low QoE).[1] Disability progression and change in function (MSFC) were not evaluated. At 2 years, similar numbers of participants in the interferon beta-1a groups and placebo groups completed the trials (RR 1.03; 95% CI, 0.98 to 1.09; 2 RCTs; moderate QoE).[1] Rates of serious adverse events were similar in the interferon beta-1a and placebo groups (RR 0.80; 95% CI, 0.52 to 1.25; meta-analysis of 4 RCTs very low QoE).[1]

Teriflunomide 7 mg and 14 mg vs. Placebo (1 RCT; 618 participants)

One fair-quality RCT compared teriflunomide 7 mg and 14 mg with placebo over 27 months in adults with a first clinical episode suggestive of MS.[1] Concerns about high loss to follow-up, author conflict of interest, and funding by industry contributed to the fair-quality assessement.[1] This trial was stopped early because of changes in the diagnostic criteria.[1] Teriflunomide significantly reduced conversion to MS (HR, 0.63; 95% CI, 0.42 to 0.95 for teriflunomide 7 mg; HR, 0.57; 95% CI, 0.38 to 0.87 for teriflunomide 14 mg; low QoE).[1] Patients in the teriflunomide groups and patients in the placebo group had similar rates of disability progression (10% for teriflunomide 7 mg [HR 0.98; 95% CI, 0.52 to 1.83 vs. placebo] vs. 7% for teriflunomide 14 mg [HR 0.70; 95% CI, 0.36 to 1.37 vs. placebo] vs. 10% placebo (very low QoE).[1] Teriflunomide significantly improved disability compared to placebo, as measured by the EDSS (mean change, -0.25 teriflunomide 7 mg vs. -0.27 teriflunomide 14 mg vs. -0.06 placebo; mean difference of -0.26 for teriflunomide 7 mg vs. placebo; mean difference of -0.23 for teriflunomide 14 mg vs. placebo; $P < .05$ for both comparisons; low QoE).[1] No significant difference in function, as measured by the MSFC was observed (low QoE).[1] Overall, 73.2% of participants in the teriflunomide 7 mg group, 75.5% in the teriflunomide 14 mg group, and 71.6% in the placebo group completed the study. Persistence was not significantly different between groups (low QoE).[1] No significant difference in serious adverse events was noted (low QoE).[1]

3. Comparative Harms from Cohort Studies

Twenty-four cohort studies compared treatment discontinuation or treatment switch by disease-modifying therapy.[1] No studies compared treatment discontinuation or treatment switch by DMD for alemtuzumab, cladribine, diroximel fumarate, ocrelizumab, ozanimod, peginterferon beta-1a, or siponimod. Data from these cohort studies are summarized in **Table 2.**

Table 2: Summary of Comparative Harms with DMD's

Outcome	Comparison	Results
Overall Discontinuation	DMF vs. interferons or glatiramer acetate (2 studies)	Favors DMF
	DMF vs. fingolimod (4 studies)	Favors fingolimod
	DMF vs. teriflunomide (1 study)	Favors teriflunomide
	DMF vs. interferons, glatiramer or fingolimod (1 study)	No difference vs. DMF
	DMF vs. interferons (1 study)	Favors DMF
	Fingolimod vs. interferons (1 study)	Favors fingolimod
	Fingolimod vs. teriflunomide (2 studies)	Favors fingolimod
	Fingolimod vs. teriflunomide (1 study)	No difference
	Glatiramer vs. interferon beta-1b (2 studies) or interferon beta-1a (1 study)	No difference
	Glatiramer vs. interferons (1 study)	Favors interferons
Discontinuation due to AEs	DMF vs. fingolimod (1 study)	Favors fingolimod
	DMF vs. teriflunomide (1 study)	No difference
	DMF vs. teriflunomide (1 study)	Favors teriflunomide
	Glatiramer vs. interferon beta-1a (1 study)	Favors glatiramer
Discontinuation due to lack of efficacy	DMF vs. teriflunomide (1 study)	Favors DMF
	Fingolimod vs. interferons (2 studies)	Favors Fingolimod
Time to discontinuation	DMF vs. interferon beta, glatiramer or teriflunomide (1 study)	No difference vs. DMF
	DMF vs. fingolimod (1 study)	Favors fingolimod
	Fingolimod vs. teriflunomide (1 study)	Favors fingolimod
	Glatiramer vs. interferon beta-1b (1 study)	No difference

Abbreviations: AE = adverse reaction; DMD = disease modifying drug; DMF = Dimethyl Fumarate

Serious Adverse Events

One cohort study found that the risk of liver injury was increased with MS therapies, including interferons and newer therapies, specifically alemtuzumab, teriflunomide, and fingolimod.[1] One cohort study evaluated the risk of PML and the analysis found that fingolimod and dimethyl fumarate were associated with an increased risk of PML.[1] Two studies evaluated infection risk. In 1 study, the rate of infections was lowest with interferon beta and glatiramer acetate.[1] Compared to no DMT, exposure to any second-generation DMT (fingolimod, dimethyl fumarate, or natalizumab) was associated with a significantly increased risk of an infection-related physician claim.[1] When assessed individually, the association was not significant for fingolimod and dimethyl fumarate.[1] One cohort study evaluating the risk of cancer found that women with MS who are treated with glatiramer acetate had an increased risk of breast cancer, though the increase was not statistically significant.[1] All individuals with MS who were treated with interferon beta showed an increased risk of non-breast cancers. The increase was not statistically significant, although the effect was large.[1] However, the evidence is from only 1 retrospective study in Israeli patients, and may not be generalizable to the U.S. Medicaid population.[1] When comparing the DMTs directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events, compared with other disease-modifying therapies assessed in the eligible trials.[1]

New Safety Alerts:

1. Thirteen worldwide cases of stroke (ischemic and hemorrhagic) or arterial dissection, occurring shortly after the patient received alemtuzumab, have been reported to the FDA since its approval in 2014 to treat relapsing forms of MS.[16] Twelve of these cases reported symptoms within 1 day of receiving alemtuzumab.[16] As a result, the FDA added a new warning about this risk in the *Warnings and Precautions* section of the prescribing information in the drug label as of November 2108.[16] The risk of stroke was also added to the existing *Boxed Warning*, the FDA's most prominent warning.[16]

2. Thirty-five cases of severely increased disability accompanied by the presence of multiple new lesions on MRI that occurred 2 to 24 weeks after fingolimod was stopped were reported to the FDA since its September 2010 approval.[16] Most patients experienced this worsening in the first 12 weeks after stopping fingolimod.[16] The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state.[16] Several patients who were able to walk without assistance prior to discontinuing fingolimod progressed to needing wheelchairs or becoming totally bedbound.[16] In patients experiencing worsening of disability after stopping fingolimod, recovery varied. Seventeen patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during fingolimod treatment.[16] As a result, the FDA added a new warning about this risk to the prescribing information of the fingolimod drug label and patient Medication Guide as of November 2018.[16]

New Formulations or Indications:

1. Monomethyl fumarate (Bafiertam™) received tentative FDA approval in November 2018 for treatment of people with relapsing MS, including CIS, RRMS, and SPMS. Dimethyl fumarate is the prodrug of monomethyl fumarate. The FDA issued final approval of monomethyl fumarate in April 2020, as Biogen's patent for dimethyl fumarate expired in June 2020. Because of its similarity to dimethyl fumarate, the FDA based the approval of monomethyl fumarate on clinical trials that demonstrated safety and efficacy of dimethyl fumarate.

2. Fingolimod (Gilenya®) received an expanded indication as of August 2019 for use in patients aged 10 years and older. Fingolimod had previously been FDA-approved for use in adults. A phase 3 trial randomly assigned patients 10 to 17 years of age with relapsing multiple sclerosis in a 1:1 ratio to receive oral fingolimod at a dose of 0.5 mg per day (0.25 mg per day for patients with a body weight of ≤40 kg) or IM interferon beta-1a at a dose of 30 mcg per week for up to 2 years.[17] The primary end point was the ARR. The mean age of the patients was 15.3 years.[17] The adjusted ARR was 0.12 with fingolimod and 0.67 with interferon beta-1a over a 2-year period (absolute difference, 0.55 relapses; relative difference, 82%; $P<0.001$).[17] Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a.[17] Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in 4 patients) and leukopenia (in 2 patients).[17] Six patients had convulsions. Serious adverse events occurred in 7 patients (6.5%) in the interferon beta-1a group and included infection (in 2 patients) and supraventricular tachycardia (in 1 patient).[17]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGEKIT	Y
interferon beta-1a	AVONEX PEN	INTRAMUSC	PEN IJ KIT	Y
interferon beta-1a/albumin	REBIF	SUB-Q	SYRINGE	Y
interferon beta-1a/albumin	REBIF REBIDOSE	SUB-Q	PEN INJCTR	Y
interferon beta-1a/albumin	AVONEX	INTRAMUSC	KIT	Y
interferon beta-1b	BETASERON	SUB-Q	KIT	Y
interferon beta-1b	EXTAVIA	SUB-Q	KIT	Y
alemtuzumab	LEMTRADA	INTRAVEN	VIAL	N
cladribine	MAVENCLAD	ORAL	TABLET	N
dalfampridine	AMPYRA	ORAL	TAB ER 12H	N
dalfampridine	DALFAMPRIDINE ER	ORAL	TAB ER 12H	N
dimethyl fumarate	TECFIDERA	ORAL	CAPSULE DR	N
diroximel fumarate	VUMERITY	ORAL	CAPSULE DR	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATIRAMER ACETATE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATOPA	SUB-Q	SYRINGE	N
interferon beta-1b	BETASERON	SUB-Q	VIAL	N
interferon beta-1b	EXTAVIA	SUB-Q	VIAL	N
ocrelizumab	OCREVUS	INTRAVEN	VIAL	N
peginterferon beta-1a	PLEGRIDY	SUB-Q	SYRINGE	N
peginterferon beta-1a	PLEGRIDY PEN	SUB-Q	PEN INJCTR	N
siponimod	MAYZENT	ORAL	TABLET	N
siponimod	MAYZENT	ORAL	TAB DS PK	N
teriflunomide	AUBAGIO	ORAL	TABLET	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 6 months

Requires PA:
- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #7
7. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
~~6.~~8. Is the prescription for teriflunomide?	**Yes:** Go to #9	**No:** Go to #11
~~7.~~9. Is the patient of childbearing potential?	**Yes:** Go to #10	**No:** Approve for up to 6 months.
~~8.~~10. Is there documentation that the patient is currently on a reliable form of contraception?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
~~9.~~11. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #12	**No:** Go to #15
~~10.~~12. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13

Approval Criteria		
~~11.~~13. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #14	**No:** Approve up to 6 months.
~~12.~~14. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
~~13.~~15. Is the prescription for a fumarate product?	**Yes:** Go to # 16	**No:** Go to #17
~~14.~~16. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
17. Is the request for cladribine?	**Yes:** Go to #18	**No:** Approve for up to 6 months
18. Is the patient of reproductive potential?	**Yes:** Go to # 19	**No:** Go to # 20
19. Is there documentation that the patient (or female partner of a male patient) is on a reliable form of contraception?	**Yes:** Go to # 20	**No:** Pass to RPh. Deny; medical appropriateness
20. Has the patient had an inadequate response to or they are unable to tolerate alternative MS treatment?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria

Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs

Generic Name	FDA Indication (Adults unless otherwise indicated)		
	CIS	**RRMS**	**SPMS**
Cladribine		X	X
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*
Siponimod	X	X	X

Ozanimod	X	X	X
Teriflunomide	X	X	X
Dimethyl Fumarate	X	X	X
Monomethyl Fumarate	X	X	X
Diroximel Fumarate	X	X	X
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis			

Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Siponimod*	X	X	X	X	X	X	
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

* sphingosine 1-phosphate receptor modulators

Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 6 hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod, ozanimod or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod or siponimod initiation with subsequent evaluations based on clinical symptoms.

- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting teriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when teriflunomide is given with other potentially hepatotoxic drugs. Consider stopping teriflunomide if serum transaminase levels increase (>3-times the upper limit of normal). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 $x10^3$ cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Fumarate salts should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:

- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

P&T/DUR Review: *8/20 (DM); 6/20; 11/17 (DM); 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

Ocrelizumab (Ocrevus™)

Goal(s):
- Restrict use of ocrelizumab in patients with relapsing-remitting multiple sclerosis (RRMS) to those who have failed multiple drugs for the treatment of RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:
- 6 to 12 months

Requires PA:
- Ocrevus™ (ocrelizumab) pharmacy or physician administered claims

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Go to #7
6. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the drug prescribed by or in consultation with a neurologist who regularly treats multiple sclerosis?	**Yes**: Approve ocrelizumab 300 mg every 2 weeks x 2 doses followed by 600mg IV every 6 months for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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

P&T/DUR Review: *6/20; 11/17 (DM); 1/17*
Implementation: *7/1/20; 1/1/18; 4/1/17*

Dalfampridine

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization:
- Up to 12 months

Requires PA:
Dalfampridine

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 Multiple Sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy previously approved by the FFS program (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the patient have moderate or severe renal impairment (est. GFR <50 mL/min)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7

Approval Criteria		
7. Is the patient ambulatory with a walking disability requiring use of a walking aid **OR;** have moderate ambulatory dysfunction and does not require a walking aid AND able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	**Yes:** Approve initial fill for 2-month trial.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking dalfampridine for ≥2 months with documented improvement in walking speed while on dalfampridine (≥20% improvement in timed 25-foot walk test)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

P&T Review: *8/20 (DM); 6/20; 11/17 (DM); 5/16; 3/12*
Implementation: *8/16, 9/1/13*

Peginterferon Beta-1a (Plegridy®)

Goal(s):

- Approve therapy for covered diagnosis that are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class. Additional information can be found at www.orpdl.org.	**No:** Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: • Adherence issues necessitating less frequent administration • Dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny for medical appropriateness.

P&T / DUR Action: *8/20 (DM); 6/20; 11/17 (DM); 9/23/14*
Implementation: *10/15*

Natalizumab (Tysabri®)

Goal(s):

- Approve therapy for covered diagnosis which are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for Jason Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing remitting multiple sclerosis (RRMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.

Approval Criteria		
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**
8. Has the patient failed to respond 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? • AND • Has the patient tried and failed a 3 month trial of Humira?	**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.

P&T / DUR Action: *8/20 (DM); 11/17 (DM)*
Implementation: *1/1/18*

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Drug Class Update with New Drug Evaluation: Serotonin Agonists (formerly Triptans)

Date of Review: August 2020

Date of Last Review: May 2019
Dates of Literature Search: 03/01/2019 - 02/27/2020
Brand Name (Manufacturer): Reyvow (Lilly USA, LLC)
Dossier Received: Yes

Generic Name: lasmiditan

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

Purpose for Class Update:
The purpose of this update is to evaluate new evidence for the serotonin agonists (previously triptan) preferred drug list (PDL) class and provide a new drug evaluation for lasmiditan.

Research Questions:
1. Is there new comparative evidence evaluating acute migraines treatments based on important outcomes (e.g., headache frequency, acute migraine medication use, reduction in number of migraines per month)?
2. Is there new comparative harms data for acute migraine 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 migraine treatments are more effective or cause less harm?
4. What is the effectiveness and harms evidence for the use of lasmiditan in the treatment of migraine?

Conclusions:
- A literature scan was recently performed for the serotonin class, therefore, new evidence was limited to one guideline and two randomized controlled trials that met inclusion criteria for the review.
- A recent guideline focused on acute migraine treatment in children and adolescents found moderate evidence of pain relief at 2 hours for oral ibuprofen and sumatriptan nasal spray (NS), which were more effective than placebo.[1] Non-prescription oral analgesics (e.g., naproxen, acetaminophen, or ibuprofen) are recommended first-line for acute migraine in children and adolescents.[1]
- Adolescents with acute migraine symptoms were found to have freedom from pain at 1 and 2 hours with zolmitriptan NS and sumatriptan/naproxen combination oral tablets (moderate to high quality evidence).[1]
- There is moderate quality evidence that zolmitriptan NS is more effective than placebo for relief of photophobia at 30 minutes (relative risk [RR] 1.66; 95% confidence interval [CI], 1.03 to 2.68).[1]

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- Lasmiditan is a newly approved oral therapy for acute migraine that works as a 5-HT_{1F} agonist (also referred to as "ditan") without vasoconstrictive properties.[5]
- Lasmiditan 200 mg, 100 mg and 50 mg were compared to placebo in 2, phase 3 studies [SPARTAN and SAMURAI (did not study 50 mg dose)]. A majority of patients, (approximately 80%) also had cardiovascular (CV) risk factors. Both studies evaluated the efficacy of lasmiditan based on a single dose that could be repeated one time within 24 hours if needed. There is low quality of evidence that all doses of lasmiditan were more effective than placebo for the primary endpoint of headache freedom at 2 hours (absolute risk reduction [ARR] 7% to 18%; number needed to treat [NNT] 6 to 14).[2,3]
- There is low quality evidence that lasmiditan 200 mg, 100 mg and 50 mg were more effective than placebo for causing freedom from the most bothersome symptom (MBS), which was a co-primary endpoint in SPARTAN and a secondary endpoint in SAMURAI.[2,3] Bothersome symptoms include: photophobia, phonophobia, nausea, or vomiting. Difference from placebo in the SPARTAN trial was 15.2% for lasmiditan 200 mg, 10.7% for lasmiditan 100 mg and 7.3% for lasmiditan 50 mg (NNT 7 to14; $p<0.05$ for all comparisons). In the SAMURIA trial the ARR was 11% and NNT of 9 for both lasmiditan 200 mg and lasmiditan 100 mg compared to placebo.
- Common adverse events associated with lasmiditan were dizziness, fatigue, paresthesia, and sedation.[4] Instructions to abstain from driving due to dizziness and somnolence associated with lasmiditan are included in the prescribing information. Severe adverse events were uncommon as this was a single episode dosing trial.

Recommendations:
- After clinical review no changes to the serotonin agonist class preferred drug list (PDL) are warranted.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
A 2019 summary of a Drug Effectiveness Review Project (DERP) report on prevention and treatment of chronic and episodic migraines reported only very low- or low-quality evidence for most outcomes. Therefore, no policy changes were made based on clinical evidence. After executive session, sumatriptan syringes and zolmitriptan tablets, rapid tablets and nasal spray were made preferred on the PDL. Preferred triptans are sumatriptan (nasal, oral and subcutaneous [SC]), oral naratriptan tablets, and zolmitriptan (tablets, rapid tabs and nasal spray). All triptans have quantity limits to ensure appropriate use. Current prior authorization (PA) criteria for topiramate requires a 90-day trial with evidence of efficacy for continued use. A majority of utilization for the triptan class is for preferred products for all formulations: nasal, oral and subcutaneous. The triptan class accounts for a small portion of overall Oregon Health Plan (OHP) fee-for-service (FFS) utilization.

Background:
Migraine is a common headache ailment characterized by debilitating headache pain, nausea, and/or light and sound sensitivity. Migraine or severe headaches have been reported in 40 million adults in the United States (US).[5] Women experience migraine more often than men.[6] Migraine severity can range from mild to severe and is known to impact quality of life, including missed work days and interference in personal relationships. Diagnosis of migraine is based on patient reported symptoms and there is a lack of objective testing options to definitively diagnose migraine. Criteria has been developed by the International Classification of Headache Disorder to help classify migraine (Table 1).[7] Migraine is commonly characterized as either episodic or chronic, based on migraine frequency.[8] Episodic migraine is defined as patients with fewer than 15 migraine or headache days per month and chronic migraine sufferers have more than 15 monthly migraine days and at least 8 are monthly migraine days.[8] Migraine may be associated with an aura, referring to the onset of sensory or motor symptoms occurring before or after headache onset.[5] Early treatment of migraine, in particular those with aura, is correlated with improved efficacy of treatment. Some factors that may dispose individuals to migraine include: emotional stress, menstruation, visual stimuli, weather changes, and certain foods or activities.[6]

Table 1. International Classification of Headache Disorders, 3rd edition (ICHD-3)[7]

Criteria for Migraine without Aura	Criteria for Migraine with Aura
A. At least 5 attacks fulfilling criteria B through D B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated) C. Headache has at least 2 of the following characteristics: • Unilateral location • Pulsating quality • Moderate to severe pain intensity • Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least on the following: • Nausea, vomiting, or both • Photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis	A. At least 2 attacks fulfilling criterion B and C B. One or more of the following fully reversible aura symptoms: • Visual • Sensory • Speech and/or language • Motor • Brainstem • Retinal C. At least three of the following six characteristics: • At least one aura symptom spreads gradually over ≥5 minutes • Two or more symptoms occur in succession • Each individual aura symptom lasts 5 to 60 minutes • At least one aura symptom is unilateral • At least one aura symptom is positive • The aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis

Treatment of migraine is divided into two types: acute (abortive) and preventative. Acute therapy is most effective when given as soon as symptoms appear and is the focus of this review. Common treatment options are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans, antiemetics and dihydroergotamines.[6] Acetaminophen and NSAIDs are recommended for mild to moderate migraine attacks that are not associated with severe nausea or vomiting. Patients that experience severe nausea or vomiting may be candidates for an oral or rectal antiemetic. Oral triptans (5-hydroxytryptamine $[HT]_{1b/1d}$ agonists) or triptan/naproxen combination products are recommended for patients with moderate to severe migraine attacks and are the most commonly used migraine specific treatment.[5] These recommendations are supported by the National Institute for Health and Care Excellence (NICE) which recommends triptans in combination with aspirin or acetaminophen, starting with the most cost-effective treatment.[9] Triptan products also have the advantage of availability in oral, NS and subcutaneous formulations. Loss of triptan efficacy over time has been reported and triptans are contraindicated in patients with cardiovascular (CV) disease.[5] Adverse events were found to be similar between the triptans by the Canadian Agency for Drugs and Technology in Health (CADTH).[10] For patients who do not tolerate triptans, ergotamine preparations are an option; however, adverse events and limited efficacy have resulted in low utilization.[5] Patients who experience a moderate to severe attack associated with vomiting or severe nausea, may benefit from SC sumatriptan, nasal sumatriptan or zolmitriptan, non-oral antiemetics and parenteral dihydroergotamine.[6] Patients with frequent attacks should be considered for preventative treatment to minimize the risk of overuse headaches which can occur when acute migraine medications are used more than 10 days per month or more than 15 days per month for aspirin, acetaminophen and NSAIDs. Treatment recommendations for children and adolescents with migraine include ibuprofen and triptans.[11]

Ditans are a new type of triptan medication that works on the $5\text{-}HT_{1F}$ receptor, void of vasoconstriction properties prompting CV warnings associated with triptan products that work as 5-HT 1 agonists.

The most commonly studied intermediate outcomes related to the acute treatment of migraine headache include: headache pain improvement, headache pain freedom (ranging from 30 minutes to 2 hours), relief of most bothersome symptom (e.g., photophobia, phonophobia, nausea, or vomiting) and need for rescue

medication. Disability, health-related quality of life, employment-related outcomes, and Patient Global Impression of Change (PGIC) are important health outcomes related to migraine. The PGIC is a scale ranging from 1-7 (very much worse to very much better) to assess the patients' rating of overall improvement. The Migraine Disability Assessment Test (MIDAS) is used to quantify headache disability based on a 7-item questionnaire. The score is based off of activity limitations ranging from little or no disability to severe disability.[5] 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.[5]

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

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

Systematic Reviews:
None identified.

New Guidelines:
High Quality Guidelines:

<u>American Academy of Neurology and American Headache Society – Acute Treatment of Migraine in Children and Adolescents</u>
In 2019 the American Academy of Neurology and American Headache Society updated guidance on management of migraine in children and adults.[1] The guideline was evaluated and met inclusion criteria according to methodological DURM standards. Placebo-controlled trials enrolling at least 90% children 0-18 years of age were included. The main outcomes evaluated were pain response at 1 hour and 2 hours, freedom from pain at 1 hour and 2 hours, and improvement in symptom outcomes. Therapies with moderate to high quality evidence are presented in Table 2. Freedom from headache pain at 1 hour was reported in adolescents receiving zolmitriptan NS 5 mg compared to placebo (RR 2.71; 95% CI, 1.54 to 4.78; based on 1 moderate quality study).[1] Sumatriptan/naproxen combination tablets demonstrated more pain-free effectiveness at 2 hours than placebo for adolescents with a RR ranging from 2.17 to 2.95 ($p<0.05$ for all doses; high quality of evidence). Zolmitriptan NS 5 mg was more effective than placebo for pain-free relief at 2 hours based on high quality of evidence (RR 1.90; 95% CI, 1.47 to 2.46).[1] Freedom from headache pain at 2 hours was reported to be more effective with sumatriptan/naproxen oral combinations and zolmitriptan NS, compared to placebo, in adolescents based on high strength of evidence. Oral ibuprofen was reported to be more effective than placebo for freedom from headache pain at 2 hours in children and adolescents based on moderate quality evidence (RR 2.15; 95% CI, 1.28 to 3.71). Sumatriptan NS was also found to more effective than placebo in this population (RR 1.46; 95% CI, 1.21 to 1.77).[1] Zolmitriptan NS and sumatriptan/naproxen oral tablets were found to relieve photophobia based on moderate quality evidence.

Guidelines recommend nonprescription oral analgesics (e.g., naproxen, acetaminophen, or ibuprofen) as an effective treatment option for acute migraine in children and adolescents. Ibuprofen (10 mg/kg) is the initial treatment recommendation in children and adolescents for acute migraine pain relief (moderate quality of evidence).[1] Sumatriptan/naproxen oral tablets, zolmitriptan NS (5 mg), sumatriptan NS (20 mg), rizatriptan orally disintegrating tablets or almotriptan are recommended for headache pain based on moderate evidence. Triptans can be combined with ibuprofen or naproxen if needed for additional pain relief. An antiemetic can be used if prominent nausea or vomiting is present.

Table 2. Acute Migraine Therapies for Children and Adults with Moderate to High Level of Evidence[1]

Treatment	Outcome	Level of Evidence
Sumatriptan 5 mg NS	Relief of nausea at 2 hours greater than placebo Relief of vomiting at 2 hours greater than placebo Pain response at 1 hour similar to placebo	Moderate
Sumatriptan 20 mg NS	Pain-free at 2 hours greater than placebo Relief of nausea at 2 hours similar to placebo Relief of vomiting at 2 hours similar to placebo	Moderate
Rizatriptan ODT 5 mg or 10 mg	Pain-free at 1 hour similar to placebo Relief of phonophobia at 2 hours similar to placebo	Moderate Moderate
Zolmitriptan 5 mg NS	Pain-free at 1 hour was greater than placebo Pain-free at 2 hours was greater than placebo Relief of vomiting at 2 hours similar to placebo	Moderate High Moderate
Zolmitriptan 20 mg NS	Pain-free at 2 hours was greater than placebo Relief of vomiting at 2 hours similar to placebo	Moderate
Combination Therapy		
Sumatriptan/naproxen OT 10/60 mg	Pain-free at 2 hours greater than placebo Relief of photophobia at 2 hours greater than placebo Relief of phonophobia at 2 hours greater than placebo	High Moderate Moderate
Sumatriptan/naproxen OT 30/180 mg	Pain-free at 2 hours greater than placebo	High
Sumatriptan/naproxen OT 85/500 mg	Pain-free at 2 hours greater than placebo Relief of nausea at 2 hours similar to placebo Relief of photophobia at 2 hours greater than placebo Relief of phonophobia at 2 hours greater than placebo	High Moderate Moderate
Ibuprofen OS 7.5-10 mg/kg	Pain-free at 2 hours greater than placebo	Moderate

Abbreviations: OS – oral solution; OT – oral tablet; NS – nasal spray

Additional Guidelines for Clinical Context:
After review, one guideline was excluded due to poor quality.[5]

New Formulations or Indications:
Sumatriptan (Tosymra): A new nasal formulation of the 5-HT $_{1B/1D}$ receptor agonist, sumatriptan, was approved by the FDA in 2019 for the acute treatment of migraine, with or without aura in adult patients.[12] A single dose of sumatriptan 10 mg NS, with a maximal dose of 30 mg in a 24-hour period separated by an hour is recommended. This formulation of sumatriptan was approved based on bioavailability equivalence to sumatriptan 4 mg subcutaneous injection.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of one citation was manually reviewed from the initial literature search. After further review, the citation was excluded because of outcome studied (eg, non-clinical).

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

Clinical Efficacy:
Lasmiditan is a 5-HT$_{1F}$ receptor agonist indicated for use in adults who have acute migraine symptoms, with or without aura (International Headache Society diagnostic criteria 1.1 and 1.2.1).[4] Two, phase 3 clinical trials contributed to the 2019 Food and Drug Administration (FDA) approval of lasmiditan, SAMURAI and SPARTAN (**Table 5**).[2,3] The average patient age was 43 years old and females represented 84% of the population in both trials. The mean baseline MIDAS score was 32.2 for the SPARTAN study and 31 for the SAMURAI study, indicating severe disability with both scores above the cutoff of 21.[13] Patients with at least one CV risk factor represented 80% patients in the SPARTAN trial and 78% in the SAMURAI trial. Preventative migraine therapy was allowed in both trials; 19% of patients in SPARTAN and 17% of patients in SAMURAI.[2,3] Important exclusion criteria included chronic headaches (more than 15 in a month) and severe comorbid conditions. Patients with orthostatic hypertension with syncope were excluded from SPARTAN and those with uncontrolled hypertension were excluded from SAMURAI. The primary endpoint for both trials was headache pain-free at 2-hours. The primary endpoint analysis included patients who had treated a migraine (full analysis set [FAS] in the SPARTAN trial and modified intent-to-treat [mITT] in SAMURAI). The SPARTAN trial had a second primary endpoint of MBS free, identified pre-dose as either nausea, photophobia, or phonophobia. Freedom from MBS was a secondary outcome in the SAMURAI trial. Photophobia was the most common MBS reported by patients in both trials. Secondary outcomes were measured in the intent-to-treat population in SPARTAN and in the mITT population in SAMURAI. Important secondary outcomes were sustained pain freedom at 24 and 48 hours.

Patients were provided with 2 doses of study drug or placebo. Patients were asked to treat a migraine that was moderate to severe and not improving within 4 hours of onset. Response to treatment was recorded over the next 48 hours in an electronic diary. Both trials evaluated symptoms, headache severity (score of 0-3), and degree of interference in normal activities and recorded at specified times: 0.5, 1, 1.5, 2, 3, 4, 24 and 48 hours post-dose.[2,3] No retrospective entries were permitted. The SPARTAN study also evaluated the PGIS score at 2 hours. Both studies allowed a second treatment dose if needed, with restrictions in

dosing that required at least 2 hours between doses and up to 24 hours after the first dose, if no other rescue treatment had been used. Patients who did not treat a migraine attack were excluded from efficacy and safety analyses.

In the SPARTAN trial, lasmiditan 200 mg, lasmiditan 100 mg and lasmiditan 50 mg were compared to placebo for the treatment of moderate-to- severe intensity migraine.[2] Time to treatment of attack was similar between all active treatment groups and placebo (approximately 1 hour). Lasmiditan 200 mg was reported to be more effective than placebo with an ARR of 18% and NNT of 6 (OR 2.3; 95% CI, 1.8 to 3.1; P<0.001).[2] Lasmiditan 100 mg and lasmiditan 50 mg were also reported to be more effective than placebo with an ARR of 10% (NNT 10) and 7% (NNT 14), respectively.[2] The co-primary endpoint of freedom from MBS was 48.7% in patients treated with lasmiditan 200mg, 44.2% with lasmiditan 100 mg, 40.8% with lasmiditan 50 mg, and 33.5% for placebo (NNT 7 to 14).[2] For the secondary endpoint of sustained pain freedom at 24 hours, all doses of lasmiditan were statistically different from placebo (ARR 4% to 9%; NNT 11 to 27). Sustained pain freedom at 48 hours was found to be more effective for only the lasmiditan 200 mg group, 19.6% of patients compared to 11.8% of patients in the placebo group (ARR 7.8%;NNT 13).[2] A second dose of medication was used in 21.2% of patients taking lasmiditan 200 mg, 26.3% of patients taking lasmiditan 100 mg, 34.4% of patients taking lasmiditan 50 mg and 39.5% taking placebo. Ninety-five percent of second doses were taken as rescue medication and the rest were for headache recurrence.[2]

In the SAMURAI trial, lasmiditan 200 mg was reported to be more effective than placebo for the primary endpoint, 32.2% and 15.3%, respectively (OR 2.6; 95% CI, 2.0-3.6; P<0.001)(ARR 17.6%/NNT 6).[3] Lasmiditan 100mg was found to be associated with freedom of headache pain at 2 hours with an absolute difference from placebo of 12% (NNT 8) (OR 2.2; 95% CI, 1.6 to 3.0; p<0.001).[3] For the secondary endpoint of freedom from the MBS, lasmiditan 200 mg and 100 mg were reported to be more effective than placebo, 40.7%, 40.9% and 29.5% (ARR of 11% and NNT of 9 for both doses). Nineteen percent of patients in the lasmiditan 200 mg group were headache pain free at 24 hours compared to 15% in the 100 mg group and 8% in the placebo group (p<0.001 for both dose comparisons).[3] Freedom from headache pain at 48 hours was also more effective in patients treated with both lasmiditan doses compared to placebo (NNT 12-14).[3] Rescue dosing was required in 31.9% of patients taking lasmiditan 200 mg, 39% of patients taking lasmiditan 100 mg, and 59.9% of patients taking placebo. Patients' results were collected up to 7 days after the migraine attack or up to 8 weeks if no attacks were experienced.

Clinical efficacy of a second dose of lasmiditan for recurrence of the initial migraine or for rescue treatment was not established. External validity of the study population was similar to what is seen in the general population with the exception of a 5:1 enrollment of women to men. This ratio is more than the general US population estimate of migraine occurring three times in as many women as men. There were also less patients with ischemic heart disease (1%) enrolled in the trials compared to the average incidence in the US. The actual number of patients with pre-existing CV disease was low in both trials and safety of using lasmiditan in this population requires further evaluation. Analysis of secondary endpoints using the ITT population in the SPARTAN trial could bias results in favor of lasmiditan, considering patients who did not treat a migraine were included. Other limitations to the evidence include lack of evidence for repeated use, efficacy beyond 2 hours, the effect of lasmiditan on decreasing frequency of migraine attacks, need for rescue therapy, and propensity to cause medication overuse headaches. There is insufficient evidence for the effect of lasmiditan on quality of life and lost work days.

Lasmiditan post marketing requirements include a pregnancy outcomes study, safety and efficacy in pediatric patients, drug interaction analysis between lasmiditan and P-gp and BCRP substrates.

Clinical Safety:
The most common adverse reactions which occurred in 5% or more of the population treated with lasmiditan were dizziness, fatigue, paresthesia, and sedation (**Table 3**). Prescribing information recommends that patients not drive for at least 8 hours after taking lasmiditan due to the risk of dizziness and somnolence.

Severe adverse events and discontinuations due to adverse events were similar between lasmiditan and placebo. There are no CV warnings in the lasmiditan labeling as a result of a low percentage of severe adverse events with a CV etiology. An important drug interaction with lasmiditan and propranolol has been reported, resulting in significant decreases in heart rate which is synergistic.[4]

Table 3. Adverse Reactions Related to Lasmiditan with a Frequency of 2% or Greater than Placebo[4]

Adverse Reaction	Lasmiditan 50 mg (N=654)	Lasmiditan 100 mg (N = 1265)	Lasmiditan 200 mg (N=1258)	Placebo (N=1262)
Dizziness	9%	15%	17%	3%
Fatigue	4%	5%	6%	1%
Paresthesia	3%	7%	9%	2%
Sedation	6%	6%	7%	2%
Nausea and/or vomiting	3%	4%	4%	2%
Muscle Weakness	1%	1%	2%	0%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Headache relief at 2 hours
2) Sustained headache relief
3) Pain free at 2 hours
4) Health related quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Pain-free at 2-hours

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Serotonin $(5\text{-HT})_{1F}$ receptor agonist
Oral Bioavailability	Given without regard to food
Distribution and Protein Binding	Distribution not described Protein Binding 55-60%
Elimination	Elimination via metabolism with ketone reduction being the major pathway
Half-Life	5.7 hours
Metabolism	Metabolism via hepatic and extrahepatic pathways primarily by non-CYP enzymes

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. Goadsby P, et al Phase 3, RCT, DB, MC, PC (SPARTAN) N=3005	1. Lasmiditan 200 mg orally as needed for moderate to severe intensity migraine* 2. Lasmiditan 100 mg orally as needed for moderate to severe intensity migraine* 3. Lasmiditan 50 mg orally as needed for moderate to severe intensity migraine* 4. Placebo orally as needed for moderate to severe intensity migraine* Treatment period: 8 weeks	Demographics: 1. Median age: 43 yo 2. 84% female 3. Mean MIDAS score: 32.2 4. Migraine with aura: 36% 5. Use of preventative migraine medications: 19% 6. ≥ 1 CV risk factor: 80% 7. ≥1 CV event: 6% Key Inclusion Criteria: 1. ≥ 18 years of age 2. ≥ 1 year history of disabling migraines (with or without aura) 3. MIDAS disability index score ≥ 11 4. Onset of migraines before the age of 50 years 5. 3-8 migraine attacks per month Key Exclusion Criteria: 1. Chronic migraine or other headaches resulting in ≥ 15 headache days per month within the past 12 months. 2. Hemorrhagic stroke 3. Epilepsy or increased risk of seizures 4. Recurrent dizziness or vertigo 5. Meniere's disease 6. Vestibular migraine 7. Vestibular disorders 8. Diabetes with complications 9. Orthostatic hypertension with syncope 10. Renal or hepatic impairment	ITT: 1. 565 2. 571 3. 598 4. 576 FAS: 1. 528 2. 532 3. 556 4. 540 Attrition: 1. 37 (6.5%) 2. 39 (6.8%) 3. 42 (7%) 4. 36 (6.3%)	Primary Endpoint: Headache pain-free at 2-hours (FAS) 1. 205 (38.8%) 2. 167 (31.4%) 3. 159 (28.6%) 4. 115 (21.3%) Lasmiditan 200 mg vs. Placebo OR 2.3 (95% CI, 1.8 to 3.1) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 1.7 (95% CI, 1.3 to 2.2) p <0.001 Lasmiditan 50 mg vs. Placebo OR 1.5 (95% CI, 1.1 to 1.9) p = 0.003 MBS-freeł (FAS) 1. 235 (48.7%) 2. 221 (44.2%) 3. 209 (40.8%) 4. 172 (33.5%) Lasmiditan 200 mg vs. Placebo OR 1.9 (95% CI, 1.4 to 2.4) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 1.6 (95% CI, 1.2 to 2.0) p <0.001 Lasmiditan 50 mg vs. Placebo OR 1.4 (95% CI, 1.1 to 1.8) p = 0.009 Secondary Endpoint (ITT population): Sustained pain freedom at 24 hours:^ 1. 128 (22.7%) 2. 102 (17.9%) 3. 103 (17.2%) 4. 77 (13.4%)	18%/ 6 10%/ 10 7%/ 14 15%/7 11%/10 7%/ 14	Study withdrawal due to AE 1. 4 (1%) 2. 1 (0.2%) 3. 0 4. 0 Serious AE 1. 1 (0.2%) 2. 1 (0.2%) 3. 0 Palpitations: 1. 2 (0.3%) 2. 2 (0.3%) 3. 2 (0.3%) 4. 1 (0.2%) Tachycardia: 1. 2 (0.3%) 2. 2 (0.3%) 3. 1 (0.2%) 4. 0 p-value not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 via central Interactive Response Technology system to receive lasmiditan or placebo for the first dose and 2:1 ratio to lasmiditan or placebo for rescue or recurrence. Patients randomized to placebo for the first dose were automatically given placebo for the second dose. Performance Bias: Low. Patients, investigators, and sponsor staff blinded to treatment allocation. Detection Bias: Unclear. Not described. Patients reported symptoms in electronic diary. Interpretation of results may be subject to bias. Attrition Bias: Low. Attrition was low and similar in all groups. Reporting Bias: High. Study was funded by manufacturer. **Applicability**: Patient: Primarily applies patients with one or more cardiac risk factors. The average number of patients with history of cardiac event that were included was low (6%) and highest in the placebo group (7.1%). Only 1% of patients had an ischemic form of CV disease, and therefore use in this population is unknown. Most patients had severe migraine scores at baseline and 95% had tried at least one prior medication for migraine. Intervention: Lasmiditan doses were appropriate and based off of phase 2 study data. Comparator: Active-treatment comparison would be more helpful to determine place in therapy. Outcomes: Outcomes are appropriate intermediate outcomes of migraine efficacy. Setting: One-hundred twenty-five headache centers in the USA, UK and Germany.

		11. Drug or alcohol abuse within the previous 3 years 12. Suicide attempt within 6 months 13. Use of more than 3 doses per month of opioids or barbiturates 14. Change of chronic migraine treatment within 3 months of study entry		Lasmiditan 200 mg vs. Placebo OR 1.9 (95% CI, 1.4 to 2.6) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 1.4 (95% CI, 1.0 to 1.9) p = 0.021 Lasmiditan 50 mg vs. Placebo OR 1.3 (95% CI, 1.0 to 1.9) p = 0.036 Sustained pain freedom at 48 hours:^ (ITT) 1. 111 (19.6%) 2. 86 (15.1%) 3. 89 (14.9%) 4. 68 (11.8%) Lasmiditan 200 mg vs. Placebo OR 1.8 (95% CI, 1.3 to 2.5) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 1.3 (95% CI, 0.9 to 1.9) p=0.058 Lasmiditan 50 mg vs. placebo OR 1.3 (95% CI, 0.9 to 1.8) P=0.065	9%/ 11 4%/ 23 3%/ 27 8%/13 NA NA			
2. Kuca, et al Phase 3, RCT, DB, MC, PC (SAMURAI) N=2231	1. Lasmiditan 200 mg orally 2. Lasmiditan 100 mg orally 3. Placebo Randomized 1:1:1 Treatment period: 8-weeks	Demographics: 1. Median age: 42 yo 2. 84% female 3. Mean MIDAS score: 31 4. Migraine with aura: 32% 5. Use of preventative migraine medications: 17% 6. ≥ 1 CV risk factor: 77.9% 7. ≥ 2 CV risk factors: 41% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Migraine diagnosis, with or without aura 3. History of disabling migraine for at least 1 year 4. MIDAS total score ≥11 5. Migraine onset before the age of 50 years	ITT: 1. 555 2. 562 3. 554 mITT: 1. 518 2. 503 3. 524 Attrition: 1. 37 (6.6%) 2. 59 (10.5%) 3. 30 (5.4%)	Primary Endpoint: Headache pain-free at 2-hours (mITT) 1. 167 (32.2%) 2. 142 (28.2%) 3. 80 (15.3%) Lasmiditan 200 mg vs. Placebo OR 2.6 (95% CI, 2.0 to 3.6) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 2.2 (95% CI, 1.6 to 3.0) p = 0.021 Secondary Endpoint: MBS-free‡ 1. 196 (40.7%) 2. 192 (40.9%) 3. 144 (29.5%)	 17%/6 13%/8	Study withdrawal due to AE 1. 0 2. 0 3. 0 Severe AE 1. 0 2 .0 3. 0 Palpitations: 1. 4 (0.7%) 2. 2 (0.3%) 3. 0 Tachycardia: 1. 0 2. 1 (0.2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via a centralized randomization process by interactive response technology, stratified by use of migraine preventative therapy. Baseline characteristics were well matched. Incidence of CV risk factors was similar to that in the general population. Performance Bias: Unclear. Lasmiditan and placebo were identical. Details on blinding of study personnel were not provided. Detection Bias: Unclear. Patients reported symptoms in electronic diary. Interpretation of results may be subject to bias. No data was provided on data analysis. Attrition Bias: Low. Attrition was low and similar between groups. Reporting Bias: High. Manufacturer funded trial.

		6. History of 3-8 migraine attacks per month (<15 headache days per month) Key Exclusion Criteria: 1. Chronic migraine history or other forms of primary or secondary chronic headache disease in the last 12 months 2. Medication-overuse headache with a headache frequency of >15 headache days per month 3. initiation or change of migraine preventative therapy within the last 3 months before screening 4. Known coronary artery disease 5. Clinically significant arrhythmia 6. Uncontrolled hypertension 7. At increased risk of seizures		Lasmiditan 200 mg vs. Placebo OR 1.6 (95% CI, 1.3 to 2.1) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 1.7 (95% CI, 1.3 to 2.2) p <0.001 Secondary Endpoint: Sustained pain freedom at 24 hours:^‡ 1. 103 (18.6%) 2. 83 (14.8%) 3. 42 (7.6%) Lasmiditan 200 mg vs. Placebo OR 2.8 (95% CI, 1.9 to 4.1) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 2.1 (95% CI, 1.4 to 3.1) p <0.001 Sustained pain freedom at 48 hours:^ 1. 91 (16.4%) 2. 84 (14.9%) 3. 42 (7.6%) Lasmiditan 200 mg vs. Placebo OR 2.4 (95% CI, 1.6 to 3.5) p < 0.001 Lasmiditan 100 mg vs. Placebo OR 2.1 (95% CI, 1.5 to 3.2) p < 0.001	11%/9 11%/9 11%/9 7%/14 9%/12 7%/14	3. 0 p-value not reported		**Applicability**: Patient: Results are most applicable to women with acute migraine. Patients with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension were excluded. Intervention: Appropriate dosing based on phase 2 trials of lasmiditan. Comparator: Placebo comparison appropriate for efficacy determination. Outcomes: Patient record of symptoms may be ambiguous. Setting: 99 centers in the United States.

Abbreviations : ADR = adverse drug event; AE = adverse effect; ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; FAS = full analysis set; ITT = intention to treat; MBS = most bothersome symptom; MC = multi-center; MIDAS = Migraine Disability Assessment; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; UK = United Kingdom; US A = United States of America; YO = years old
Key: * A second dose was permitted 2 to 24 hours after initial dosing if needed for rescue or recurrence of migraine; ł Most bothersome symptom (MBS) was identified pre-dose as either nausea, photophobia, or phonophobia; ^ Sustained pain freedom is defined as being pain-free 2 hours after the first dose, and at the assigned time assessment, and not having used any medication after the first dose; ‡ Considered an exploratory endpoint due to type I error.

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Appendix 1: Current Preferred Drug List

Triptans, Nasal

Generic	Brand	Form	PDL
sumatriptan	IMITREX	SPRAY	Y
sumatriptan	SUMATRIPTAN	SPRAY	Y
sumatriptan	TOSYMRA	SPRAY	Y
zolmitriptan	ZOMIG	SPRAY	Y
sumatriptan succinate	ONZETRA XSAIL	AER POW BA	N

Triptans, Oral

Generic	Brand	Form	PDL
naratriptan HCl	AMERGE	TABLET	Y
naratriptan HCl	NARATRIPTAN	TABLET	Y
naratriptan HCl	NARATRIPTAN HCL	TABLET	Y
sumatriptan succinate	IMITREX	TABLET	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	TABLET	Y
zolmitriptan	ZOLMITRIPTAN ODT	TAB RAPDIS	Y
zolmitriptan	ZOMIG ZMT	TAB RAPDIS	Y
zolmitriptan	ZOLMITRIPTAN	TABLET	Y
zolmitriptan	ZOMIG	TABLET	Y
almotriptan malate	ALMOTRIPTAN MALATE	TABLET	N
eletriptan hydrobromide	ELETRIPTAN HBR	TABLET	N
eletriptan hydrobromide	RELPAX	TABLET	N
frovatriptan succinate	FROVA	TABLET	N
frovatriptan succinate	FROVATRIPTAN SUCCINATE	TABLET	N
rizatriptan benzoate	MAXALT MLT	TAB RAPDIS	N
rizatriptan benzoate	RIZATRIPTAN	TAB RAPDIS	N
rizatriptan benzoate	MAXALT	TABLET	N
rizatriptan benzoate	RIZATRIPTAN	TABLET	N
sumatriptan succ/naproxen sod	SUMATRIPTAN SUCC-NAPROXEN SOD	TABLET	N
sumatriptan succ/naproxen sod	TREXIMET	TABLET	N
lasmiditan	REYVOW	TABLET	N

Triptans, Subcutaneous

Generic	Brand	Form	PDL
sumatriptan succinate	IMITREX	CARTRIDGE	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	CARTRIDGE	Y
sumatriptan succinate	ALSUMA	PEN INJCTR	Y
sumatriptan succinate	IMITREX	PEN INJCTR	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	PEN INJCTR	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	SYRINGE	Y
sumatriptan succinate	IMITREX	VIAL	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	VIAL	Y
sumatriptan succinate	SUMAVEL DOSEPRO	NDL FR INJ	N
sumatriptan succinate	ZEMBRACE SYMTOUCH	PEN INJCTR	N

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 27, 2020

Search Strategy:

#	Searches	Results
1	sumatriptan.mp. or Sumatriptan/	3140
2	zolmitriptan.mp.	636
3	naratriptan.mp.	332
4	almotriptan.mp.	281
5	eletriptan.mp.	285
6	frovatriptan.mp.	204
7	rizatriptan.mp.	506
8	1 or 2 or 3 or 4 or 5 or 6 or 7	4133
9	limit 8 to (english language and humans and yr="2019 -Current")	15
10	limit 9 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	1
11	sumatriptan.mp. or Sumatriptan/	3140
12	zolmitriptan.mp.	636

13	naratriptan.mp.	332
14	almotriptan.mp.	281
15	eletriptan.mp.	285
16	frovatriptan.mp.	204
17	rizatriptan.mp.	506
18	11 or 12 or 13 or 14 or 15 or 16 or 17	4133
19	limit 18 to (english language and humans and yr="2019 -Current")	15
20	limit 19 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	1

Appendix 4: Prescribing Information Highlights

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

REYVOW (lasmiditan) tablets, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

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

REYVOW™ is a serotonin (5-HT) 1F receptor agonist indicated for the acute treatment of migraine with or without aura in adults. (1)

Limitations of Use

REYVOW is not indicated for the preventive treatment of migraine. (1)

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

- The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. (2)
- No more than one dose should be taken in 24 hours. (2, 5.1)

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

Tablets: 50 mg, 100 mg (3)

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

- None. (4)

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

- Driving Impairment: Advise patients not to drive or operate machinery until at least 8 hours after taking each dose of REYVOW. Patients who cannot follow this advice should not take REYVOW. Patients may not be able to assess their own driving competence and the degree of impairment caused by REYVOW. (5.1)
- Central Nervous System (CNS) Depression: REYVOW may cause CNS depression and should be used with caution if used in combination with alcohol or other CNS depressants. (5.2, 7.1)
- Serotonin Syndrome: Reactions consistent with serotonin syndrome were reported in patients treated with REYVOW. Discontinue REYVOW if symptoms of serotonin syndrome occur. (5.3)
- Medication Overuse Headache: Detoxification may be necessary. (5.4)

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

Most common adverse reactions (≥5% and > placebo) were dizziness, fatigue, paresthesia, and sedation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- REYVOW may further lower heart rate when administered with heart rate lowering drugs. (7.3)
- Avoid concomitant use with P-gp and Breast Cancer Resistant Protein (BCRP) substrates. (7.4)

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

- Based on animal data, may cause fetal harm. (8.1)
- REYVOW has not been studied in patients with severe hepatic impairment (Child-Pugh C) and its use in these patients is not recommended. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: MM/YYYY

Appendix 5: Key Inclusion Criteria

Population	Children, adolescents and adults with acute migraine
Intervention	5-HT agonists
Comparator	Active treatment or placebo
Outcomes	Pain freedom, freedom from most bothersome symptom, quality of life
Timing	Study of any duration
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Antimigraine ~~–~~ ~~Triptans~~Serotonin Agonists

Goal(s):

- Decrease potential for medication overuse headache through quantity limits and therapeutic duplication denials.
- Promote PDL options.

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [1]
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Check the Reason for PA:

- Non-Preferred drugs will deny on initiation
- Preferred drugs will deny only when maximum dose exceeded
- Both will deny for concurrent therapy (concurrent triptans by different routes is allowed)

Quantity Limits per Labeling.

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per Month
Almotriptan	Axert	25 mg	6.25 mg tab 12.5 mg tab	12 tabs
Eletriptan	Relpax	80 mg	20 mg tab 40 mg tab (blister pack 6, 12)	6 tabs
Frovatriptan	Frova	7.5 mg	2.5 mg tab (blister pack 9)	9 tabs
Lasmiditan	Reyvow	200 mg	50 mg tab 100 mg tab	8 tabs
Naratriptan	Amerge	5 mg	1 mg tab 2.5 mg tab (blister pack 9)	9 tabs
Rizatriptan	Maxalt Maxalt MLT	30 mg	5 mg tab 10 mg tab (blister pack 6, 12)	12 tabs
Sumatriptan tablets	Imitrex & generics	200 mg	25 mg tab, 50 mg tab, 100 mg tab (blister pack 9)	9 tablets
Sumatriptan nasal spray	Imitrex & generics	40 mg	5 mg, 10 mg (box of 6)	18 spray units
Sumatriptan nasal powder	Onzetra Xsail	44 mg	22 mg (11 mg in each nostril)	6 nosepieces
Sumatriptan injectable	Imitrex & generics	12 mg	6 mg/0.5 mL	6 vials
Sumatriptan injectable	Sumavel	12 mg	6 mg/0.5 mL units (package of 6)	6 jet injectors
Sumatriptan injectable	Zembrace Symtouch	12 mg	3 mg/0.5 mL (package of 4)	12 auto-injectors

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per Month
Sumatriptan /naproxen	Treximet	170/1000 mg (2 tablets)	85/500 mg tab (box of 9)	9 tablets
Zolmitriptan	Zomig Zomig ZMT	10 mg	2.5 mg tab (blister pack, 6)	6 tabs
Zolmitriptan nasal spray	Zomig NS	10 mg	5 mg (box of 6)	3 packages (18 spray units)

Abbreviations: d = days; MR = may repeat; NS = nasal spray; PO = orally

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of migraine headaches?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is requested drug a preferred product?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA within recommended dose limits. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and dose limits.	**No:** Go to #5

Approval Criteria		
5. Is request for a higher dose than listed in quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness. • May recommend use of migraine prophylactic therapy and reinforce that doses above those recommended by the manufacturer increase the incidence of medication overuse headache. • One lifetime 90-day taper may be approved at pharmacist's discretion. • Document.	**No:** Trouble-shoot claim payment (e.g., days' supply?). Go to #6.
6. Is the request for two different oral triptans concurrently?	**Yes:** Go to #7	**No:** Approve for 6 months
7. Is this a switch in Triptan therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and override for concurrent use for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *8/20 (KS), 5/19 (KS); 3/16; 3/10; 9/09; 11/03; 5/03*
Implementation: *5/1/16, 3/23/10; 1/1/10; 7/1/06; 5/31/05; 6/30/04*

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

OHSU Drug Effectiveness Review Project Summary Report - Calcitonin Gene-Related Peptide Inhibitors

Date of Review: August 2020

Date of Last Review: May 2019
Literature Search: 08/01/18-06/17/20

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

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 quality of life?
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)?
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 2020 Drug Effectiveness Review Project (DERP) report on CGRP inhibitors.[1] Drugs included in the review are eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant (**Table 1**). Evidence suggests modest efficacy for the prevention of migraine and treatment of acute migraine and small differences in quality of life scores, with improvements of less than 10%.[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 1.8 to 3.5 days a month) compared to placebo. [1]
- Quality of life was improved, compared to placebo, with the use of eptinezumab, erenumab, fremanezumab and galcanezumab based on moderate quality of evidence.

*Episodic Migraine Prevention (**Table 3**)*
- The number of migraine days per month were reduced with eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, difference ranging from -0.7 to -2.8 days (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.

*Acute Migraine Treatment **(Table 4**)*
- For the outcome of freedom from pain at 2 hours rimegepant and ubrogepant were more effective than placebo, by a difference of 6.4% to 16.6% more patients experiencing pain freedom, based on moderate quality of evidence.[1]

Author: Kathy Sentena, PharmD

Cluster Headache Prevention

- Galcanezumab was more effective for the prevention of cluster headache compared to placebo with 3.5 (95% CI, -0.2 to -6.7) fewer attacks per week, for weeks 1-3 (low quality of evidence).[1] There is low quality evidence from one randomized trial that there is no difference between galcanezumab and placebo in cluster headache prevention at week 8.
- There was only low quality of evidence available for the comparison of adverse events between CGRP inhibitors and placebo for all treatment studied. Adverse events, severe adverse events and discontinuations due to adverse events were similar to placebo for the majority of CGRP inhibitors.
- There is insufficient evidence for the use of CGRP inhibitors in different subgroups and evidence of use beyond 24 weeks.

Recommendations:

- After clinical review no changes to the PDL are warranted.
- Update prior authorization (PA) criteria to include acute migraine treatments, rimegepant and ubrogepant, and indication for cluster headache for galcanezumab.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- A review in May of 2019 maintained 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. There are no preferred therapy options.
- There were 33 claims for CGRP inhibitors of quarter 1 of 2020 for Oregon Health Plan (OHP) Fee-for-Service (FFS) population. Each claim represents a significant cost to the OHP.

Methods:

The April 2020 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.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

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. There are 6 CGRP inhibitors approved for migraine treatment in adults **(Table 1).**

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

Drug	Manufacturer	Dose	Approval Date	Approved Indication	Number of identified Studies
Eptinezumab VYEPTI	Alder Biopharmaceuticals, Inc.	100 mg or 300 mg IV every 3 monthsł	February 2020	Migraine Prevention	3
Erenumab AIMOVIG	Amgen	70 mg or 140 mg SC every monthł	May 2018	Migraine Prevention	6
Fremanezumab AJOVY	Teva Pharmaceuticals	225 mg SC monthly or 675 mg SC every 3 months	September 2019	Migraine Prevention	5
Galcanezumab* EMGALITY	Eli Lilly	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Prevention	6
Rimegepant ZYDIS	Biohaven Pharmaceuticals	75 mg orally as needed for acute migraine attack	February 2020	Acute Migraine Treatment	3
Ubrogepant UBRELVY	Allergan	50 mg, 100 mg orally as needed for acute migraine attack	December 2019	Acute Migraine Treatment	4

Abbreviations: IV – intravenously; SC – subcutaneously

Key: * Initial loading dose of 240 mg followed by a monthly dose of 120 mg; ł Some patients may benefit from the 300 mg dose

The purpose of this DERP report is to update evidence for the use of CGRP inhibitors since the last published update in October 2018.[1] Literature was searched through March 31, 2020. Main outcomes of interest were migraine events (symptoms, function, disability and quality of life), use of rescue therapies, employment related outcomes, health care utilization and adverse events. Quality of life assessment tools used for the determination of headache severity were the 6-item Headache Impact Test (HIT-6), Migraine-specific Quality of Life Score (MSQL) and Migraine Disability Assessment (MIDAS). 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”. Higher HIT-6 scores are related to a greater impact on quality of life with a range of 36-78 points. A change of 2.3 units has been suggested as the minimal clinically important difference (MCID). 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. 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. The MIDAS test is used to quantify headache disability based on a 7-item questionnaire. The score is based off of activity limitations ranging from little or no disability to severe disability. 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. For many of the quality of life assessments there are not well defined minimal clinically important differences related to the treatment effect. A total of 14 new randomized controlled trials were identified, to bring the total trial inclusion number to 27. All trials but one was placebo-controlled and there was insufficient evidence for the direct comparison of CGRP inhibitors. The quality of studies was considered fair, with the exception of 1 poor quality trial.

Chronic Migraine Prevention

Eptinezumab, erenumab, fremanezumab, and galcanezumab are used for the prevention of chronic migraine.[1] With the exception of fremanezumab, all other therapies were studied in one randomized controlled trial. Patients in the studies had a mean of 14.1 to 19.6 migraine days per month. Outcomes with moderate evidence are presented in **Table 2**.[1] All of the therapies were found to be more effective than placebo for the outcomes of number of migraine days per month, days with acute medication use per month, and for the percent of patients with a 50% reduction in migraine days. The evidence for serious adverse events and discontinuations due to adverse events were associated with low or very low quality of evidence.

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

Outcome	Results	Quality of Evidence	Evidence Conclusion
Eptinezumab (every 3 months) vs. Placebo			
Migraine days per month	<u>*Dodick et al*</u> Eptinezumab 300 mg vs. Placebo -2.7 days (95%CI, -4.4 to -0.9) P=0.003 Eptinezumab 100 mg vs. Placebo -2.1 days (95% CI, -3.8 to -0.4) P=0.018 Eptinezumab 30 mg vs. Placebo -2.4 days (95% CI, -4.0 to -0.7) P=0.005 Eptinezumab 10 mg vs. Placebo -1.2 days (95% CI, -2.9 to 0.6) P=0.180	Moderate	Eptinezumab 30 mg, 100 mg and 300 mg are more effective than placebo for reducing the number of migraine days per month by an approximate decrease of 2 days.
Percentage of patients with at least 50% reduction in number of migraine days per month	<u>*Dodick et al*</u> Eptinezumab 300 mg single dose: 38 (33.3%) Eptinezumab 100 mg single dose: 37 (31.4%) Eptinezumab 30 mg single dose: 33 (28.2%) Eptinezumab 10 mg single dose: 33 (26.8%) Placebo: 24 (20.7%) Eptinezumab 300 mg vs. Placebo P=0.033 Eptinezumab 100 mg vs. Placebo P=0.072	Moderate	Eptinezumab 300 mg was more effective than placebo for the odds of a patient experiencing at least a 50% decrease in number of migraine days per month (ARR 12.6%/NNT 8)

	Eptinezumab 30 mg vs. Placebo P=0.201 Eptinezumab 10 mg vs. Placebo P=0.294		
Mean change in HIT-6	*Dodick et al* Eptinezumab 300 mg vs. Placebo -4.2 points (95%CI, -6.3 to -2.1) P<0.001 Eptinezumab 100 mg vs. Placebo -1.1 points (95% CI, -3.1 to 0.88) P=0.27 Eptinezumab 30 mg vs. Placebo -0.7 points (95% CI, -2.7 to 1.3) P=0.49 Eptinezumab 10 mg vs. Placebo -0.7 points (95% CI, -2.7 to 1.3) P=0.50	Moderate	Eptinezumab 300 mg was more effective than placebo at improving HIT-6 scores by approximately 4 points (5% change)
Erenumab (monthly) vs. Placebo			
Mean change in migraine days per month	*Tepper et al* Erenumab 70 mg vs. Placebo: -2.5 (95% CI, -3.5 to -1.4) P<0.0001 Erenumab 140 mg vs. Placebo: -2.5 (95% CI, -3.5 to -1.4) P<0.0001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the number of migraine days by 2.5 days per month
Days with acute migraine medication use per month	*Tepper et al* Erenumab 70 mg vs. Placebo: -1.9 (95% CI, -2.6 to -1.1) P<0.0001 Erenumab 140 mg vs. Placebo: -2.6 (95% CI, -3.3 to -1.8)	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the need for migraine medication days per month by approximately 2 days

	P<0.0001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Tepper et al* Erenumab 70 mg vs. Placebo: OR 2.2 (95% CI, 1.5 to 3.3) P=0.0001 Erenumab 140 mg vs. Placebo: OR 2.3 (95% CI, 1.6 to 3.5) P<0.0001	Moderate	Erenumab 70 mg and 140 mg were more effective at increasing the odds of a patient experiencing at least 50% reduction in number of migraine days
Mean change in HIT-6 of 5 points or greater	*Tepper et al* Erenumab 70 mg vs. Placebo: OR 2.3 (95% CI, 1.5 to 3.4) P< 0.001 Erenumab 140 mg vs. Placebo: OR 2.3 (95% CI, 1.5 to 3.4) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in improving HIT-6 scores by ≥ 5 points
Fremanezumab (monthly) vs. Placebo			
Migraine days per month	*Bigal et al** Fremanezumab 225 mg vs. Placebo -1.7 days (95% CI, -3.7 to 0.2) P=0.08 Fremanezumab 900 mg vs. Placebo -2.0 days (95% CI, -3.9 to -0.1) P=0.04 *Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.1 days P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.8 days P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo -3.1 days (95% CI, -3.8 to -2.4)	Moderate	Fremanezumab 225 mg, 675 mg, 900 mg were more effective than placebo in reducing migraine days by 2-3 days per month; however, one study of the 225 mg strength found no statistically significant difference between placebo and active treatment

	P<0.0001 Fremanezumab 225 mg monthly vs. Placebo -3.5 (95% CI, -4.2 to -2.8) P<0.001		
Days with acute migraine medication use per month	*Bigal et al** Fremanezumab 225 mg vs. Placebo -2.2 (95% CI, -4.0 to 0.3) P=0.02 Fremanezumab 900 mg vs. Placebo -2.0 (95% CI, -3.9 to -0.20) P=0.03 *Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.3 days P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.8 days P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo -3.1 days (95% CI, -3.8 to -2.4) P<0.0001 Fremanezumab 225 mg monthly vs. Placebo -3.4 (95% CI, -4.0 to -2.7) P<0.0001	Moderate	Fremanezumab 225 mg, 675 mg and 900 mg were more effective than placebo reducing the number of days with acute migraine medication use per month
Percentage of patients with at least 50% reduction in number of migraine days per month	*Silberstein et al** Fremanezumab 225 mg: 153 (41%) Placebo: 67 (18%) RR 2.3 (95% CI, 1.8 to 2.9) P<0.001 Fremanezumab 675 mg quarterly:	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo at increasing the odds of a patient experiencing at least 50% reduction in the number of migraines days per month

	141 (38%) Placebo: 67 (18%) RR 2.1 (95% CI, 1.6 to 2.7) P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo OR 5.8 (95% CI, 3.6 to 9.6) P<0.0001 Fremanezumab 225 mg monthly vs. Placebo 5.8 (95% CI, 3.6 to 9.5) P<0.001		
Mean change in HIT-6	*Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.4 points P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.9 days P<0.001	Moderate	HIT-6 scores were improved with fremanezumab 225 mg and 675 mg more than those treated with placebo by 2 points (3% change)
Galcanezumab (monthly) vs. Placebo			
Migraine days per month	*Detke et al* Galcanezumab 120 mg vs. Placebo -2.1 days (95% CI, -2.9 to -1.3) P<0.001 Galcanezumab 240 mg vs. Placebo -1.9 days (95% CI, -2.7 to -1.1) P<0.001	Moderate	Galcanezumab 120 mg and 240 mg were more effective than placebo in reducing migraine days by approximately 2 days per month
Percentage of patients with at least 50% reduction in number of migraine days per month	*Detke et al* Galcanezumab 120 mg vs. Placebo OR 2.1 (95% CI, -1.6 to -2.8) P<0.001 Galcanezumab 240 mg vs. Placebo OR 2.1 (95% CI, 1.6 to 2.8) P<0.001	Moderate	The odds of a patient experiencing at least a 50% reduction in number of migraine days per month was higher in patients treated with galcanezumab 120 mg and 240 mg compared to placebo

Days with acute headache days per month	<u>*Detke et al*</u> Galcanezumab 120 mg vs. Placebo -2.5 days (95% CI, -3.3 to -1.8) P<0.001 Galcanezumab 240 mg vs. Placebo -2.0 days (95% CI, -2.8 to -1.3) P<0.001	Moderate	Galcanezumab 120 mg and 240 mg were more effective than placebo in reducing the number of acute headache days by approximately 2 days per month
Mean change in MSQL (functioning-preventive score)	<u>*Detke et al*</u> Galcanezumab 120 mg vs. Placebo 7.0 (95% CI, 4.2 to 9.8) P<0.001 Galcanezumab 240 mg vs. Placebo 5.1 (95% CI, 2.3 to 7.9) P<0.001		Galcanezumab 120 mg and 240 mg improved functioning more than placebo by approximately 6%

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; HIT-6 – Six-item Headache Impact Test; MD – mean difference; MSQL – Migraine Specific Quality of Life Score; OR – odds ratio; RR – relative risk

Key: * Patients in the 225 mg group were given fremanezumab 675 mg at baseline and 225 mg of fremanezumab at weeks 4 and 8; † Patients in the fremanezumab 225 mg group received an initial dose of 675 mg

Episodic Migraine Prevention

Drugs studied for episodic migraine prevention include eptinezumab, erenumab, fremanezumab, and galcanezumab. Patients had a history of 6.6 to 11.3 migraine 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 approximately 2 days (**Table 3**). The evidence for serious adverse events and discontinuations due to adverse events were similar to placebo (low quality of evidence).

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

Outcome	Results	Quality of Evidence	Evidence Conclusions
Eptinezumab (every 3 months) vs. Placebo			
Migraine days per month	<u>*Ahina et al*</u> Eptinezumab 30 mg vs. Placebo -0.82 (95% CI, -1.39 to -0.25) P=0.0046 Eptinezumab 100 mg vs. Placebo -0.69 (95% CI, -1.25 to -0.12) P=0.02	Moderate	Eptinezumab 30 mg, 100 mg, 300 mg and 1000 mg were more effective than placebo in reducing migraine days by approximately 1 day per month

	Eptinezumab 300 mg vs. Placebo -1.11 (95% CI, -1.68 to -0.54) P=0.0001 *Dodick et al* Eptinezumab 1,000mg vs. Placebo -1.0 days (95% CI, -2.0 to 0.1) P=0.0306		
Percentage with at least 50% reduction in number of migraine days per month	*Ahina et al* Eptinezumab 30 mg vs. Placebo 12.8% (95% CI, 3.7% to 21.5%) ARR 12.8%/NNT 8 P=0.006 Eptinezumab 100 mg vs. Placebo 12.4% (95% CI, 3.2% to 21.5%) ARR 12.4%/NNT 8 P=0.009 Eptinezumab 300 mg vs. Placebo 18.9% (95% CI, 9.8% to 28.0%) ARR 18.9%/NNT 5 P=0.0001 *Dodick et al* Eptinezumab 1,000mg: 56 (73%) Placebo: 52 (67%) RR 1.15 (95% CI, 0.94 to 1.41) P=0.21	Moderate	Eptinezumab 30 mg, 100 mg and 300 mg were more effective than placebo at increasing the odds of patients experiencing at least 50% reduction in number of migraine days per month with a benefit of 12% to 19% patients (NNT 5-17)
Erenumab (monthly) vs. Placebo			
Migraine days per month	*Reuter et al* Erenumab 140 mg vs. Placebo -1.6 (95% CI, -2.7 to -0.5) P=0.004 *Sakai et al* Erenumab 70 mg vs. Placebo -2.3 (95% CI, -3.0 to -1.6)	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the number of migraine days per month by approximately 2 days

	P<0.001 Erenumab 140 mg vs. Placebo -1.9 (95% CI, -2.6 to -1.2) P<0.001 *Dodick et al* Erenumab 70 mg vs. Placebo -1.0 (95% CI, -1.6 to -0.5) P<0.001 *Goadsby et al* Erenumab 70 mg vs. Placebo -1.4 (95% CI, -1.9 to -0.9) P<0.001 Erenumab 140 mg vs. Placebo -1.9 (95% CI, -2.3 to -1.4) P < 0.001 *Sun et al* Erenumab 70 mg vs. Placebo -1.1 (95% CI, -2.1 to -0.2) P=0.02		
Days with acute migraine medication use per month	*Reuter et al* Erenumab 140 mg vs. Placebo -1.7 (95% CI, -2.4 to -1.0) P<0.001 *Sakai et al* Erenumab 70 mg vs. Placebo -2.1 (95% CI, -2.7 to -1.5) P<0.001 Erenumab 140 mg vs. Placebo -2.0 (95% CI, -2.6 to -1.5) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the days with acute migraine medication use per month by approximately 2 days

	Dodick et al Erenumab 70 mg vs. Placebo -0.6 (95% CI, -1.0 to -0.2) P=0.002 *Goadsby et al* Erenumab 70 mg vs. Placebo -0.9 (95% CI, -1.2 to -0.6) P < 0.001 Erenumab 140 mg vs. Placebo -1.4 (95% CI, -1.7 to -1.1) P < 0.001 *Sun et al* Erenumab 70 mg vs. Placebo -1.0 (95% CI, -1.6 to -0.3) P=0.004		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Reuter et al* Erenumab 140 mg vs. Placebo OR 1.7 (95% CI, -2.4 to -1.0) P<0.001 *Sakai et al* Erenumab 70 mg vs. Placebo OR 5.6 (95% CI, 2.6 to 12.1) P<0.001 Erenumab 140 mg vs. Placebo OR 4.7 (95% CI, 2.2 to 10) P<0.001 *Dodick et al* Erenumab 70 mg: 112 (39.7%) Placebo: 85 (29.5%) OR 1.59 (95% CI, 1.12 to 2.27) P=0.01	Moderate	Erenumab 70 mg and 140 mg were more effective in percentage of patients with at least 50% reduction in the number of migraine days per month

	Goadsby et al Erenumab 70 mg: 135 (43.3%) Placebo: 84 (26.6%) OR 2.13 (95% CI, 1.52 to 2.98) P<0.001 Erenumab 140 mg: 159 (50.0%) Placebo: 84 (26.6%) OR 2.81 (95% CI, 2.01 to 3.94) P<0.001 *Sun et al* Erenumab 70 mg: 46 (46%) Placebo: 43 (30%) OR 2.0 (95% CI, 1.2 to 3.4) P=0.01		
Mean change in HIT-6	*Sakai et al* Erenumab 70 mg vs. Placebo -2.1 points (95% CI, -3.3 to -0.9) P<0.001 Erenumab 140 mg vs. Placebo -2.0 points (95% CI, -3.2 to -0.8) P=0.001 *Dodick et al* Erenumab 70 mg vs. Placebo -2.3 points (95% CI, -3.3 to -1.3) P<0.001 *Goadsby et al* Erenumab 70 mg vs. Placebo -2.1 points (95% CI, -3.0 to -1.1) P<0.001 Erenumab 140 mg vs. Placebo -2.3 points (95% CI, -3.2 to -1.3) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective at improving HIT-6 scores compared to placebo by approximately 2 points (3% change)

	Sun et al Erenumab 70 mg vs. Placebo -1.0 points (95% CI, -2.5 to -0.6) P=0.22		
Fremanezumab (monthly) vs. Placebo			
Migraine days per month	*Bigal et al* Fremanezumab 225 mg vs. Placebo -2.8 days (95% CI, -4.1 to -1.6) P-value not reported Fremanezumab 675 mg vs. Placebo -2.6 days (95% CI, -3.9 to -1.3) P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -1.5 days (95% CI, -2.0 to -0.93) P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.3 days (95% CI, -1.8 to -0.72) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in reducing the number of migraine days per month by approximately 2 days
Days with acute headache medication use per month	*Bigal et al* Fremanezumab 225 mg vs. Placebo -1.8 (95% CI, -2.9 to -0.66) P-value not reported Fremanezumab 675 mg vs. Placebo -1.7 (95% CI, -2.8 to -0.60) P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -1.4 days (95% CI, -1.8 to -0.89) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in reducing the days with acute headache medication use per month by 1- 2 days

	Fremanezumab 675 mg quarterly vs. Placebo -1.3 days (95% CI, -1.8 to -0.82) P<0.001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Bigal et al* Fremanezumab 225 mg: 53 (56%) Fremanezumab 675 mg: 55 (57%) Placebo: 36 (35%) Fremanezumab 225 mg vs. Placebo RR 1.61 (95% CI, -.17 to 2.22) P=0.003 Fremanezumab 675 mg vs. Placebo RR 1.66 (95% CI, 1.21 to 2.27) P=0.002 *Dodick et al* Fremanezumab 225 mg monthly: 137 (47.7%) Fremanezumab 675 mg quarterly: 128 (44.4%) Placebo: 81 (27.9%%) Fremanezumab 225 mg vs. Placebo RR 1.71 (95% CI, 1.37 to 2.13) P<0.001 Fremanezumab 675 mg vs. Placebo RR 1.59 (95% CI, 1.27 to 2.99) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in increasing the percent of patients with at least 50% reduction in number of migraine days per month
Mean change in MIDAS score	*Bigal et al* Fremanezumab 225 mg vs. Placebo -14.5 points (95% CI, -26.8 to -2.2) P-value not reported Fremanezumab 675 mg vs. Placebo -15.2 points (95% CI, -27.6 to -2.8)	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in improving quality of life, based on a change in MIDAS score of 5-15 points

	P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -7.0 points (95% CI, -10.5 to -3.5) P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -5.4 points (95% CI, -8.9 to -1.9) P=0.002		
Galcanezumab (monthly) vs. Placebo			
Migraine days per month	*Dodick et al* Galcanezumab 150 mg every 2 weeks vs. Placebo MD -1.2 (95% CI, -1.9 to -0.6) P=0.003 *Ksljarevski et al* Galcanezumab 120 mg monthly MD -2.0 days (95% CI, -2.6 to -1.5) P=0.026 Galcanezumab 240 mg monthly MD -1.9 days (95% CI, -2.4 to -1.4) P=0.026 *Skljarevski et al* Galcanezumab 120 mg v. Placebo -0.9 (no CI provided) P=0.02 Galcanezumab 300 mg -0.9 (no CI provided) P=0.02 *Stauffer, et al* Galcanezumab 120 mg vs. Placebo	Moderate	Galcanezumab 120 mg, 150 mg, 240 mg and 300 mg reduced the number of migraine days per month by approximately 1-2 days compared to placebo

	-1.9 (95% CI, -2.5 to -1.4) P<0.001 Galcanezumab 240 mg vs. Placebo -1.8 (95% CI, -2.3 to -1.2) P<0.001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Dodick et al* Galcanezumab 150 mg: 69 (70.4%) Placebo: 47 (45.2%) OR 2.88 (95% CI, 1.61 to 5.18) *Skljarevski et al* Galcanezumab 120 mg: 137 (59.3%) Galcanezumab 240 mg: 126 (56.5%) Placebo: 233 (36.0%) Galcanezumab 120 mg vs. Placebo RR 1.65 (95% CI, 1.40 to 1.94) P=0.025 Galcanezumab 240 mg vs. Placebo RR 1.57 (95% CI, 1.33 to 1.86) P=0.025 *Skljarevski et al* Galcanezumab 120 mg: 47 (75.8%) Galcanezumab 300 mg: 78 (61.9%) RR 1.22 (95% CI, 1.01 to 1.49) P=0.07 *Stauffer et al* Galcanezumab 120 mg: 131 (62.3%) Galcanezumab 240 mg: 127 (60.9%) Placebo: 164 (95% CI, 38.6%) Galcanezumab 120 mg vs. Placebo OR 2.6 (2.0 to 3.4) P<0.001	Moderate	Galcanezumab 120 mg, 150 mg, 240 mg and 300 mg increased the percentage of patients with at least 50% reduction in number of migraine days per month

	Galcanezumab 240 mg vs. Placebo OR 2.5 (95% CI, 1.9 to 3.2) P<0.001		
Mean change in MIDAS score	*Ksljarevski et al* Galcanezumab 120 mg monthly -9.2 points (95% CI, -11.8 to -6.6) P<0.001 Galcanezumab 240 mg monthly -8.2 points (95% CI, -10.5 to -5.9) P<0.001 *Stauffer et al* Galcanezumab 120 mg vs. Placebo -6.3 points (no CI reported) P<0.001 Galcanezumab 240 mg vs. Placebo -5.2 points (no CI reported) P<0.002	Moderate	Mean change in MIDAS scores were more improved in patients taking 120 mg and 240 mg compared to placebo

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; HIT-6 – Six-item Headache Impact Test; MD – mean difference; MIDAS – Migraine Disability Assessment; NNT – number needed to treat; OR – odds ratio; RR – relative risk

Acute Migraine Treatment

Rimegepant and ubrogepant are two new CGRP inhibitors used for the acute treatment of migraine. Both therapies were studied in 3 randomized controlled trials (Table 4).[1] 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.

Table 4. CGRP Inhibitors for Acute Migraine Treatment[1]

Outcome	Results	Quality of Evidence	Evidence Conclusions
Rimegepant vs. Placebo			
Freedom from pain at 2 hours post-dose	*Marcus et al* Rimegepant 75 mg: 27 (31.4%) Placebo: 32 (15.3%) RR 2.1 (95% CI, 1.3 to 3.2) P<0.05	Moderate	Rimegepant 75 mg was more effective than placebo in increasing the number of patients who were free from pain at 2 hours (by approximately 15%) and was similar in efficacy to sumatriptan 75 mg

	Rimegepant 75 mg: 27 (31.4%) Sumatriptan: 35 (35.0%) RR 0.90 (95% CI, 0.6 to 1.4) P-value not reported *Croop et al* Rimegepant 75 mg vs. Placebo RD 10.4 (95% CI, 6.5 to 14.2) P<0.0001 *Lipton et al* Rimegepant 75 mg: 105 (19.6%) Placebo: 64 (12.0%) RR 1.6 (95% CI, 1.2 to 2.2) P<0.001		
Freedom from most bothersome symptom at 2 hours post-dose	*Croop et al* Rimegepant 75 mg vs. Placebo RD 8.3 (95% CI, 3.4 to 13.2) P=0.0009 *Lipton et al* Rimegepant 75 mg: 202 (37.6%) Placebo: 135 (25.2%) RR 1.5 (95% CI, 1.3 to 1.8) P<0.001	Moderate	Rimegepant 75 mg was more effective than placebo in the number of patients with freedom from the most bothersome symptom at 2 hours
Ubrogepant vs. Placebo			
Freedom from pain at 2 hours post-dose	*Voss et al* Ubrogepant 50 mg: 22 (21.0%) Placebo: 10 (8.9%) RR 2.4 (95% CI, 1.2 to 4.7) *Dodick et al* Ubrogepant 50 mg: 81 (19.2%) Placebo: 54 (11.8%) OR 1.83 (95% CI, 1.25 to 2.66) P=0.01	Moderate	Freedom from pain at 2 hours was higher, by an average of 9%, in the number of patients taking ubrogepant 50 mg and 100 mg compared to placebo

	Ubrogepant 100 mg: 95 (21.2%) Placebo: 54 (11.8%) OR 2.04 (95% CI, 1.41 to 2.95) P<0.001 *Lipton et al* Ubrogepant 50 mg: 101 (21.8%) Placebo: 65 (14.3%) OR 1.62 (95% CI, 1.14 to 2.29) P=0.01		
Freedom from most bothersome symptom at 2 hours post-dose	*Dodick et al* Ubrogepant 50 mg: 162 (38.6%) Placebo: 126 (27.8%) OR 1.70 (95% CI, 1.27 to 2.28) P=0.002 Ubrogepant 100 mg: 169 (39.7%) Placebo: 126 (27.8%) OR 1.63 (95% CI, 1.22 to 2.17) P=0.02 *Lipton et al* Ubrogepant 50 mg: 180 (38.9%) Placebo: 125 (27.4%) OR 1.65 (95% CI, 1.25 to 2.20) P=0.01	Moderate	Freedom from the most bothersome symptom at 2 hours was higher in patients taking ubrogepant 50 mg and 100 mg compared to placebo
Ability to function normally within 2 hours post-dose	*Dodick et al* Ubrogepant 50 mg: 171 (40.6%) Placebo: 136 (29.8%) OR 1.67 (95% CI, 1.22 to 2.27) P-value not reported Ubrogepant 100 mg: 192 (42.9%) Placebo: 136 (29.8%) OR 1.93 (95% CI, 1.42 to 2.61) P-value not reported	Moderate	Ubrogepant 50 mg and 100 mg were more effective than placebo at improving ability to function normally within 2 hours

Abbreviations: CI – confidence interval; OR – odds ratio; RD – risk difference; RR – risk ratio

CGRP Inhibitors for Cluster Headache Prevention
Galcanezumab was studied for the use of cluster headache prevention in one randomized controlled trial.[1] There was low quality evidence of no difference between groups at 8 weeks.

Evidence Limitations
Evidence was downgraded due manufacturer sponsorship and involvement in the trials themselves. Some studies were also biased due to imprecision because of infrequent event occurrence. Trials were of short duration preventing long-term evidence for efficacy and harms in a condition that is treated on a chronic basis.

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; 2020.

Appendix 1: Current Preferred Drug List

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

Table 1. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
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
Ubrogepant	Acute migraine treatment

Length of Authorization:

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

Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonists (eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant) pharmacy and physician administered claims

Covered Alternatives:

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

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

Approval Criteria		
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for 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 #5
5. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7
7. Is the request for acute migraine treatment AND the patient is an adult?	**Yes:** Go to #12	**No:** Go to #8
~~5.~~8. Is the request for the prevention of cluster headache AND the patient is an adult?	**Yes:** Go to #14	**No:** Go to #9
~~6.~~9. Is there documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult?	**Yes:** Document migraine days per month _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~7.~~10. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	**Yes:** Document agents used and dates _____ _____ Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
~~8.~~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
~~9. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?~~	~~**Yes:** Approve for 3 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
12. Has the patient failed adequate trials (3 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; recommend triptan trial
13. 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
~~10.~~14. Does the patient have at least 4 headache attacks per week AND have a history of cluster headaches beyond one month?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
15. Has the patient failed at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, frovatriptan, prednisone, subocciptal steroid injection, topiramate, and valproate)?	**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
~~3.~~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 (e.g. minimum 2 doses for treatment given every 3 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 reduction of at least 8 cluster headaches per week?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 11/1/2018

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Drug Class Update: Topical Analgesics and Anesthetics

Date of Review: August 2020

Date of Last Review: (analgesics) July 2018 (DERP), January 2016; (anesthetics) none
Dates of Literature Search: 11/01/15–03/17/2020

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

Purpose for Class Update: The purpose of this class update is to evaluate new evidence for the safety and effectiveness of topical analgesics in relieving acute and neuropathic pain. In addition, the safety and effectiveness of topical anesthetics in relieving acute pain prior to procedures and venous catheter insertion will be reviewed.

Research Questions:
1. What is the comparative efficacy and effectiveness of topical analgesics (diclofenac, capsaicin, salicylates and lidocaine) for acute and chronic pain?
2. What are the comparative harms of topical analgesics (diclofenac, capsaicin, salicylates, and lidocaine) for acute and chronic pain?
3. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of topical analgesics (diclofenac, capsaicin, salicylates, and lidocaine) for acute and chronic pain?
4. What is the comparative efficacy and effectiveness of topical anesthetics (lidocaine, tetracaine, and prilocaine) when used prior to procedures or venous catheter insertion?
5. What are the comparative harms of topical anesthetics (lidocaine, tetracaine, and prilocaine) when used prior to procedures or venous catheter insertion?
6. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in the benefits and harms of topical anesthetics (lidocaine, tetracaine, and prilocaine)?

Conclusions:
Topical Analgesics
- Five recently published systematic reviews were identified for this class update. Four reviews focused on efficacy and safety of topical diclofenac, capsaicin, lidocaine, and salicylate in acute and chronic pain management for adults.[1-4] One systematic review evaluated safety of topical non-steroidal anti-inflammatory drugs (NSAIDs) used for pain associated with osteoarthritis (OA).[5] One recently published guideline included recommendations for use of topical analgesics in OA.[6]
- A 2016 Cochrane review evaluated safety and efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) for chronic musculoskeletal pain in adults.[1] In a pooled analysis of studies lasting 6 to 12 weeks, topical diclofenac was more effective than placebo for 50% pain reduction in chronic pain (Risk Ratio

[RR] 1.2, 95% Confidence Interval [CI] 1.1 to 1.3, Number Needed to Treat [NNT] 10; moderate-quality evidence).[1] A few trials compared a topical NSAID to an oral NSAID in patients with knee OA, but overall they showed similar efficacy (low-quality evidence).[1] There was an increase in local adverse events (mostly mild skin reactions) with topical diclofenac compared with placebo or oral NSAIDs (RR=1.8, 95% CI 1.5 to 2.2, Number Needed to Harm [NNH] 16; moderate quality evidence).[1]

- A 2017 Cochrane review examined safety and efficacy of high-concentration (8%) topical capsaicin for chronic neuropathic pain in adults.[2] In a pooled analysis of 4 trials, more participants with postherpetic neuralgia (PHN) reported having improved pain relief greater than 50% with high-concentration capsaicin compared to low-concentration (0.04%) capsaicin at 8 to 12 weeks (RR 1.44, 95% CI 1.12 to 1.86, NNT 9; moderate quality evidence).[2] Two pooled studies evaluated pain relief in patients with human immunodeficiency virus (HIV)-neuropathy and reported average pain intensity reductions of at least 30% over baseline with capsaicin 8% compared to capsaicin 0.04% (active control) over 2 to 12 weeks (RR 1.35, 95% CI 1.09 to 1.68, NNT 11; very low quality evidence).[2] One study in patients with diabetic peripheral neuropathy (DPN) and another study in participants with persistent pain following inguinal herniorrhaphy did not show a difference between capsaicin and placebo for pain reduction (very low quality evidence).[2] Adverse event withdrawals did not differ between groups, based on small numbers of events (moderate quality evidence).[2]
- A 2017 Cochrane review pooled data from 13 systematic reviews to evaluate the safety and efficacy of topical analgesics (NSAIDs, salicylate rubefacients, capsaicin, and lidocaine) for treatment of acute and chronic pain in adults.[3] The review found superior efficacy of 3 diclofenac formulations compared to placebo in reducing acute pain when used for 1 week, based on moderate quality evidence: Flector® plaster (RR 1.5, 95% CI 1.4 to 1.7, NNT 5), Voltaren Emulgel™ (RR 3.8, 95% CI 2.7 to 5.5, NNT 2) and other types of diclofenac plaster (RR 1.6, 95% CI 1.4 to 1.8, NNT 4).[3] In chronic musculoskeletal pain, the review found topical diclofenac gel and plaster reduced pain compared to placebo for durations less than 6 weeks based on moderate to high-quality evidence (RR 1.9, 95% CI 1.5 to 2.3, NNT 5) and for durations greater than 6 weeks (RR 1.2, 95% CI 1.1 to 1.3, NNT 10).[3] The review found topical capsaicin 8% was efficacious in reducing pain due to PHN compared to placebo based on moderate-quality evidence (RR 1.3, 95% CI 1.0 to 1.7, NNT 11).[3] Efficacy of topical salicylate, low-concentration (0.04%) capsaicin, and lidocaine was not well supported by evidence, and lacked evidence of effect in reducing pain associated with acute or chronic pain conditions.[3]
- The safety assessment from the 2017 Cochrane review on topical analgesics reported systemic or local adverse event (AE) rates with topical NSAIDs (4.3%) did not differ from topical placebo (4.6%) in patients with acute pain (RR 0.98, 95% CI 0.8 to 1.2; high quality evidence).[3] More local adverse events occurred with topical diclofenac (14%) than placebo (8%) in chronic pain conditions (RR 1.8, 95% CI 1.5 to 2.2, NNH 16; moderate-quality evidence).[3] Local pain with topical high-concentration capsaicin occurred more frequently (10%) than with placebo (4%) in patients with neuropathic pain (RR 2.4, 95% CI 1.4 to 4.1, NNH 16; moderate quality evidence).[3] Local AEs with topical capsaicin 0.04% (63%) were higher than topical placebo (24%) in people with chronic pain (RR 2.6, 95% CI 2.1 to 3.3, NNH 3; high quality evidence).[3]
- A 2019 Cochrane review evaluated the safety and efficacy of topical NSAIDs in relieving acute musculoskeletal pain in adults.[4] Ten studies (n=2050) compared topical diclofenac formulations with placebo.[4] In the pooled analysis, the proportion of participants experiencing successful treatment (50% pain reduction) with topical diclofenac was 74% compared to 47% of placebo-treated participants (RR 1.6, 95% CI 1.5 to 1.7, NNT 4).[4] Fifteen studies (n=3271) provided adequate data to analyze local AE with diclofenac. Similar AE rates were reported by 3.1% of patients who used topical diclofenac compared with 4.3% of patients who received placebo (RR 0.78, 95% CI 0.56 to 1.1).[4]
- A 2019 systematic review assessed the safety of topical NSAIDs in the management of OA in an analysis of randomized, placebo-controlled trials.[5] Eight studies with low risk of bias compared topical diclofenac with placebo were included in the meta-analysis.[5] Overall, there were more AEs with topical diclofenac compared with placebo (Odds Ratio [OR] 1.30, 95% CI 1.10 to 1.53; high quality evidence).[5] Study withdrawals due to AEs were also higher with topical diclofenac compared with placebo (OR 2.00, 95% CI 1.27 to 3.14; high quality evidence).[5]

- The American College of Rheumatology/Arthritis Foundation (ACR/AF) 2019 guideline on the management of OA of hand, hip, and knee updated their 2012 recommendations.[6] Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.[6] Topical low-concentration (0.04%) capsaicin is conditionally recommended for patients with knee OA and conditionally recommended against use in patients with hand OA.[6] Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.[6]
- No new evidence was identified to assess differences in benefits and harms for topical analgesics in specific subgroups of patients based on demographics, socioeconomic status, comorbidities, or pregnancy.

Topical Anesthetics

- A 2012 Cochrane systematic review examined the evidence from 6 randomized controlled trials (RCTs) involving 343 participants with leg ulcer pain using an eutectic mixture of local anesthetics (EMLA) cream compared to a placebo cream prior to ulcer debridement.[7] Participants who received EMLA had lower pain ratings based on the 0 to 100 mm visual analog scale (VAS) (mean difference [MD] -20.65 mm, 95% CI -12.19 to -29.11, $p < 0.00001$; moderate quality evidence) during ulcer debridement.[7] No significant differences between groups in burning or itching were observed.[7]
- A 2017 Cochrane review focused on safety and efficacy of topical anesthetics for pain control during repair of dermal laceration.[8] There was insufficient evidence to compare efficacy of topical anesthetics versus infiltrated local anesthesia.[8] The second objective, to compare the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal lacerations, found no significant differences between formulations, but the available data had high risk of bias.[8] The overall low-quality of the evidence for this review was due to limitations in design and implementation, imprecision of results, and high probability of publication bias (selective reporting of data).[8] Additional well-designed RCTs with low risk of bias are necessary before definitive conclusions regarding comparative safety and efficacy of topical anesthetics for pain control during dermal laceration repair can be reached.[8]
- There is insufficient evidence to assess differences in benefits and harms for topical anesthetics in specific subgroups of patients based on demographics, socioeconomic status, or comorbidities.

Recommendations:

- Rename the topical analgesic class as “topical pain medications” and add topical anesthetics to this new PDL class.
- Given the insufficient comparative evidence for safety and efficacy, designate at least 1 topical anesthetic with an indication for a funded condition on the Health Evidence Review Commission (HERC) prioritized list as preferred agents in the topical pain medications class on the Practitioner-Managed Prescription Drug Plan (PMPDP) based on drug costs in the executive session.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy:

A literature scan focused on safety and efficacy of topical analgesics was presented to the Pharmacy and Therapeutics (P and T) Committee at the January 2016 meeting. The scan found moderate-quality evidence supporting the short-term use of topical NSAIDs as safe and effective treatment options for acute musculoskeletal pain. The comparative safety and efficacy of topical capsaicin and lidocaine in managing neuropathic pain were summarized in a Drug Effectiveness Review Project (DERP) summary report presented to the P and T Committee at the July 2018 meeting. The strength of evidence for most outcomes within the report was low or insufficient, as data came from single studies and were imprecise.[9] In July 2018, the P and T Committee approved a quantity limit of 3 topical lidocaine patches per day to ensure safe use. Prior authorization (PA) Criteria for the lidocaine patch are included in **Appendix 4.** Preferred topical analgesics on the PMPDP include capsaicin cream and diclofenac drops. Non-preferred medications include diclofenac patch, diclofenac gel, capsaicin patch, lidocaine cream, lidocaine patch, and diclofenac/capsicum oleoresin. **Appendix 1** includes a list of the topical analgesics included on the preferred drug list (PDL)

Approximately 50 Oregon Health Plan (OHP) fee-for-service (FFS) patients had claims for topical analgesics in the first quarter of 2020. Most of the claims for preferred medications in the topical analgesic class were for capsaicin (30%) Most of the approved claims for nonpreferred medications were for diclofenac gel (48%) and lidocaine patches (20%).

Topical anesthetics (lidocaine, prilocaine, tetracaine, and benzocaine) have not been reviewed by the P and T Committee and the medications in this class do not currently have PDL status. As there are similar drugs in the topical analgesic and topical anesthetic classifications, both medication classes are included in this update.

Background:

Topical Analgesics

Commonly used topical analgesics applied to intact skin include salicylate rubefacients, capsaicin, lidocaine, and diclofenac. Indications for topical analgesics include pain relief for acute conditions such as sprains or strains and management of chronic pain associated with neuralgia or osteoarthritis (OA).[10] Management of OA with topical diclofenac is supported by moderate quality evidence, but there is less robust evidence for capsaicin and salicylates.[11] Salicylates are related pharmacologically to aspirin and NSAIDs, but when used topically their principal action is as counter-irritants.[12] Counter-irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves.[12] Topical salicylates are approved for temporary relief of minor aches and pains of muscle and joints associated with OA, sprains, and strains. However, a 2014 Cochrane review concluded available evidence does not support the use of topical rubefacients containing salicylates for acute injuries or chronic conditions.[13] The low quality of evidence means that uncertainty remains regarding the efficacy of salicylate-containing rubefacients in relieving acute and chronic pain.[13]

Topical application of capsaicin results in desensitization of the sensory axons and inhibition of pain transmission.[12] Topical capsaicin creams and patches are available in formulations ranging from 0.025% to 0.1% and are indicated for temporary relief of minor aches and pain of muscles and joints. The 2014 Veterans Administration/Department of Defense (VA/DoD) OA guidelines recommend topical capsaicin as an alternative to topical NSAIDs for knee OA.[11] The VA/DoD recommendations are based on moderate quality evidence that a small net benefit has been observed with topical capsaicin in knee OA.[11] There is insufficient evidence for pain relief with capsaicin in hip OA.[11] The National Institute for Health and Clinical Excellence (NICE) guidelines for OA management also include topical capsaicin as a possible adjunct to treatments for knee or hand OA.[14] The 2013 NICE guidance for treatment of neuropathic pain in adults suggests capsaicin cream for people with localized postherpetic neuralgia (PHN) who wish to avoid, or who cannot tolerate, oral treatments.[15]

The high-concentration (8%) capsaicin patch is approved by the Food and Drug Administration (FDA) to treat PHN.[16] In 2012, the FDA denied application of an expanded indication for neurpathic pain from HIV for the 8% capsaicin patch.[16] The 8% patch, which remains on skin for 60 minutes and is readministered no more frequently than 3 months, can only be administered by a health care professional. Patients must be pretreated with a topical anesthetic and monitored for adverse effects at least 2 hours after administration. The treatment setting needs to be well ventilated due to vaporization of capsaicin, as cough due to inhalation of capsaicin vapors is a hazard for both healthcare professionals and patients.[12] To date, no guidelines recommend the use of high-concentration capsaicin for initial management of PHN.

Topical lidocaine dampens peripheral nociceptor sensitization and decreases central nervous system hyperexcitability which prevents transmission of pain signals.[12] The topical lidocaine 5% patch is FDA-approved for relief of pain associated with PHN and requires a prescription. The 4% over-the-counter patch is approved for temporary relief of minor localized pain. Lidocaine does not cross intact skin well, and when applied as a patch, the amount of lidocaine that

penetrates is enough to cause analgesia, but not anesthesia.[17] Canadian Pain Society guidelines recommend topical lidocaine as a fourth-line agent for management of PHN.[18]

Topical NSAIDs penetrate the skin and underlying tissues where they inhibit cyclooxygenase (COX) enzymes, thus reducing pain and inflammation.[12] The rationale behind topical application is based on the ability of NSAIDs to inhibit COX enzymes locally, with minimum systemic uptake.[12] Their use is therefore limited to conditions where the pain is superficial and localized, such as in joints and skeletal muscle.[12] Guidance from a 2014 NICE publication recommends topical NSAIDs for patients with mild to moderate OA of the knee or hand, particularly in patients with few affected joints and/or a history of sensitivity to oral NSAIDs.[14] The NICE guidelines also state that topical NSAIDs should be considered before oral therapies and salicylate rubefacients should not be considered for treating OA.[14] Diclofenac is the only topical NSAID available in the United States (U.S). Clinical trials of topical formulations of diclofenac have shown significantly superior efficacy compared to placebo and similar efficacy to oral NSAIDs in reducing pain associated with acute injuries.[19] A comparative summary of topical analgesics is provided in **Table 1**.

Table 1.Topical Analgesic Preparations[20,21]

Topical Agent	Mechanism of Action	FDA Approved Indications	Comments
Diclofenac Patch, Cream, Gel and Solution (1% to 2%)	COX-2 inhibition	-Acute pain due to strains, sprains and contusions -OA Pain	-Bears same FDA-mandated warnings regarding gastrointestinal, cardiovascular, and hepatic risks as oral NSAIDs -Minimal systemic absorption
Trolamine Salicylate 10% cream	Counterirritant: desensitizes pain receptors	Acute Musculoskeletal Pain	-No trial data demonstrating efficacy in OA. -Excessive use or ingestion is associated with toxicity. -Available over-the-counter
Capsaicin Cream, Gel, Liquid, Patch and Lotion (0.025% to 0.1%)	Counterirritant: desensitizes pain receptors	-OA Pain -Musculoskeletal Pain	-Application site pain and burning early in treatment have been reported -Local irritation may be intolerable -Concerns about whether desensitization of nerve fibers is reversible -Available over-the counter
Capsaicin 8% Patch	Counterirritant: desensitizes pain receptors	Postherpetic Neuralgia	-Must be administered by a healthcare professional under close supervision -Requires pre-treatment with a local anesthetic and patient post-application monitoring for up to 2 hours -Treatment may be repeated every 3 months -May apply up to 4 simultaneus patches
Lidocaine 5% Patch	Blocks neuronal impulses	Postherpetic Neuralgia	-Application site reactions have been reported -May apply up to 3 simultaneus patches

Lidocaine Cream, Ointment, Gel and Patch (2% to 4%)	Blocks neuronal impulses	Acute Pain	Available over-the-counter
Abbreviations: COX-2= Cycloxygenase-2; FDA=Food and Drug Administration, NSAID=Non-steroidal anti-inflammatory drug; OA=osteoarthritis			

Topical Anesthetics

Topical anesthetics (lidocaine, benzocaine, prilocaine, and tetracaine) are approved for use in alleviating pain associated with hemorrhoids, sore throat, dermal irritation (i.e., pruritic eczemas, insect bites, sunburns, and abrasions of the skin), mouth and gum irritation, acute pain relief prior to procedural repair or prior to venous catheter insertion.[20,21] According to the Oregon HERC prioritized list, the following conditions are not funded: minor burns (line 605), uncomplicated hemorrhoids (line 621), and contact dermatitis (line 533).[22] This review will focus on use of topical anesthetics in funded conditions including peri-procedural local anesthesia and intravenous (IV) cannulation.

A laceration is a deep cut or tear in the skin or soft tissue often caused by blunt trauma, incision by a sharp object, or mammalian bite.[8] Anesthetics interrupt the transmission of electrical impulses along nerves by inactivating sodium channels.[8] Local anesthetics including lidocaine and bupivacaine injection are used for peri-procedural pain management of laceration repair.[8] Topical anesthetics may be used in children or patients who cannot tolerate injections.[8] Topical anesthetics such as lidocaine, tetracaine, or prilocaine may be combined with a vasoconstrictor such as epinephrine or cocaine. The addition of the vasoconstrictor prevents systemic absorption of the topical anesthetic. Commonly used options include: EMLA cream (2.5% lidocaine/2.5% prilocaine), lidocaine/tetracaine 7%/7% patch or cream, and lidocaine 4% cream. Some commercially available topical anesthetics become effective in 30 minutes, however, the combination of lidocaine/prilocaine may have a delayed onset of 60 minutes.[23]

The largest safety concern with topical anesthetics has been the risk of methemoglobinemia, particularly when there is prolonged use of larger than recommended doses.[24] Prescribing guidance recommends an EMLA dose should be limited to 1 to 2 g of cream per 10 cm^2 to infants older than 3 months, and weighing at least 5 kilograms to avoid toxicity.[24] Similar age and weight-based dosage regimens are recommended to avoid toxicity with other topical anesthetics.[24] **Table 2** summarizes information about the various topical anesthetics that are approved for use in HERC funded conditions.

Table 2. Common Topical Anesthetic Preparations[20,21]

Agent	Dose	Onset of Action (minutes)	Duration of Action (minutes)	Comments
Liposomal lidocaine (LMX_4)	LMX_4 (liposomal lidocaine 4%) ▪ Age <4 years: 1 gram applied to appropriate site (6.25 cm^2 of skin). ▪ Age ≥4 years: 1 to 2.5 gram applied to appropriate site (6.25 cm^2 of skin). Supplied as 5 g, 15 g, and 30 g tube	30	60 to 120	Available over-the-counter May cause methemoglobinemia with excessive application or in patients with predisposition to methemoglobinemia (e.g., glucose-6-phosphate dehydrogenase (G6PD) deficiency or taking methemoglobin-inducing medication).

Self-heating lidocaine and tetracaine patch (Synera) and topical cream (Pliaglis)	Lidocaine 7% and Tetracaine 7% ▪ Apply one patch to intact skin for 20 to 30 minutes and promptly remove. After one failed attempt, one additional patch may be applied in children. Simultaneous application of more than one patch is not recommended in children ≤12 years Supplied as 50 cm^2 patch or 30 g and 100 mg tubes of cream	20 to 30	90	Prolonged application of the patch to intact skin or application to broken skin or mucous membranes may result in serious local anesthetic toxicity. Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia.
Lidocaine-prilocaine (eutectic mixture of local anesthetics [EMLA], Lidopril, Prilovix) cream	Lidocaine 2.5% and Prilocaine 2.5% Adult Dose: 2 grams/10cm^2 of skin Pediatric dosing is based on patient weight. Supplied as 5 g and 30 g tube.	60	60 to 120	Infants under 3 months of age should monitored for methemoglobinemia before, during and after topical application of lidocaine-prilocaine. Methemoglobinemia has been reported with use of local anesthetics; increased risk in patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites and other drugs associated with methemoglobinemia.

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:

Topical Analgesics

Cochrane: Topical Non-steroidal Anti-Inflammatory Drugs for Chronic Musculoskeletal Pain in Adults

A 2016 Cochrane review updated a previous 2012 evaluation of topical NSAIDs for chronic musculoskeletal pain in adults.[1] New evidence published through February 2016 was included in the update. Randomized, double-blind, active or placebo-controlled trials in which treatments were administered to adults with moderate intensity musculoskeletal pain of at least 3 months duration met inclusion critiera.[1] The primary outcome was clinical success, defined as at least a 50% reduction in pain.[1] Secondary outcomes included adverse events and trial withdrawals due to adverse events or lack of efficacy. Five new studies were included in the update, which expanded the total number of studies to 39. Diclofenac and ketoprofen were the only two topical NSAIDs with good quality and longer duration studies, mostly in people aged over 40 years with painful knee arthritis.[1] Oral NSAIDs that served as active comparators included diclofenac, celecoxib, and ibuprofen; however most of the trials compared a topical NSAID to placebo. For pooled analyses, studies were generally of moderate or high methodological quality, although some trials were at risk of bias due to short duration and small population size.[1]

In a pooled analysis of studies lasting 6 to 12 weeks, topical diclofenac was modestly more effective than placebo for 50% pain reduction (RR 1.2, 95% CI 1.1 to 1.3, NNT 10, 6 trials, moderate quality evidence).[1] Four studies of 6 to 12 weeks duration demonstrated topical ketoprofen gel was modestly more successful in reducing OA knee pain compared to placebo (OR 1.22, 95% CI 1.03 to 1.45, NNT 7; moderate-quality evidence).[1] A few trials compared a topical NSAID to an oral NSAID in patients with knee OA, but overall they showed similar efficacy (low-quality evidence).[1]

Nineteen studies reported information on local adverse events with topical diclofenac and ketoprofen.[1] There was an increase in local adverse events (mostly mild skin reactions) with topical diclofenac compared with placebo or oral NSAIDs (RR 1.8, 95% CI 1.5 to 2.2, NNH 16, 15 studies; moderate-quality evidence). Reporting of systemic adverse events (such as gastrointestinal upset) was poor, but where reported there was no difference between topical NSAID and placebo (very low quality evidence).[1] Serious adverse events were infrequent and not different between topical NSAIDs and placebo (very low-quality evidence).[1]

Cochrane: Topical Capsaicin (High Concentration) For Chronic Neuropathic Pain in Adults

A 2017 Cochrane review updated a 2013 summary of high concentration (8%) topical capsaicin patch for chronic neuropathic pain in adults.[2] Databases were searched through June 2016 for this update. Two new studies (n=415) met inclusion criteria, bringing the total number of studies to 8, which involved a total of 2,488 participants.[2] Participants had pain due to PHN, HIV-neuropathy, DPN, and persistent pain after inguinal herniorrhaphy.[2] The duration of application of the high-concentration topical capsaicin patch varied between 30 and 90 minutes, with most participants treated for 60 minutes.[2] Efficacy outcomes reflecting moderate (improved) to substantial (very much improved) pain relief after a single drug application were based from the Patient Global Impression of Change (PGIC) at specific timepoints, usually 8 and 12 weeks.[2] Other outcomes included average pain scores over weeks 2 to 12, the number of participants with pain intensity reduction of at least 30% or at least 50% over baseline, and information on adverse events and study withdrawals. Two studies used a placebo control and six used low dose (0.04%) topical capsaicin as an active control to help maintain blinding.[2] Efficacy outcomes were inconsistently reported, resulting in analyses for most outcomes being based on incomplete data.[16] Five trials were judged to have low or unclear risk of bias, and one study was judged to have a high risk of bias.[2]

Four studies (n=1272) evaluated people with PHN.[2] At both 8 and 12 weeks about 10% more participants reported much improved or very much improved pain relief greater than 50% with high-concentration (8%) capsaicin compared to low-concentration (0.04%) capsaicin (RR 1.44, 95% CI 1.12 to 1.86, NNT 9; moderate-quality evidence).[2] More participants (about 10%) had average 8-week and 12-week pain intensity reductions over baseline of at least 30% (RR 1.42, 95% CI 1.10 to 1.84, NNT 10) and at least 50% (RR 1.55, 955 CI 1.20 to 1.99, NNT 12) with capsaicin than control (very low-quality evidence).[2]

Two studies (n=801) evaluated people with painful HIV-neuropathy. One study reported the proportion of participants who were much improved or very much improved at 12 weeks (27% with high-concentration capsaicin and 10% with active control).[2] For both studies, more participants had average pain intensity reductions over baseline of at least 30% with capsaicin than control over 2 to 12 weeks (RR 1.35, 95% CI 1.09 to 1.68, NNT 11, very low-quality evidence).[2] One very low quality study (n=369) reported on patients with DPN and noted more participants were much or very much improved with 30% pain reduction at 8 and 12 weeks, but the results were not statistically significant (RR 1.2, 95% CI 0.92 to 1.6).[2] One small study of 46 participants with persistent pain following inguinal herniorrhaphy did not show a difference between capsaicin and placebo for pain reduction (very low-quality evidence).[2] The quality of the evidence was downgraded due to sparse data, imprecision, possible effects of imputation methods, and susceptibility to publication bias.[2]

Local adverse events were common, but not consistently reported. Serious adverse events were no more common with capsaicin 8%(3.5%) than capsaicin 0.04% (3.2%).[2] Adverse event withdrawals did not differ between groups, but lack of study withdrawals due to lack of efficacy were somewhat more common with control than active treatment, based on small numbers of events (six to eight studies, 21 to 67 events; moderate-quality evidence, downgraded due to few events).[2] No deaths were judged to be related to study medication.[2]

Cochrane: Topical Analgesics for Acute and Chronic Pain in Adults

A 2017 Cochrane review analyzed 13 systematic reviews evaluating analgesic efficacy and associated adverse events of topical analgesics (NSAIDs, salicylate rubefacients, capsaicin, and lidocaine) for the treatment of acute and chronic pain in adults.[3] Systematic reviews in acute and chronic pain published to February 2017 were included in the review.[3] The primary outcome was at least 50% pain relief (participant-reported) at an appropriate duration. Withdrawals due to lack of efficacy or adverse events, systemic and local adverse events, and serious adverse events were also assessed. Pain relief in 3 distinct clinical conditions were considered for this review: 1) acute musculoskeletal conditions (sprains, strains, or muscle pain), 2) OA, rheumatoid arthritis, or other chronic musculoskeletal conditions, and 3) neuropathic pain. The 13 Cochrane reviews (206 studies with around 30,700 participants) assessed the efficacy and harms from a range of topical analgesics for management of acute and chronic pain conditions.[3] Most reviews concentrated on evidence comparing topical analgesic to topical placebo products; comparisons between topical and oral analgesics were rare.[3] Management of acute pain with topical therapy was evaluated in 4 systematic reviews.[12] Twelve reviews addressed management of chronic pain with topical agents.[12] All 13 reviews met AMSTAR criteria.[3]

In acute musculoskeletal pain with assessment at about 7 days, therapies included topical diclofenac, piroxicam, and ketoprofen.[3] Evidence was moderate- to high-quality for the acute pain conditions treated for 1 week.[3] Three topical formulations of diclofenac were compared to placebo and showed superior efficacy in reducing pain: Flector® plaster (RR 1.5, 95% CI 1.4 to 1.7, NNT 5) , Voltaren Emulgel™ (RR 3.8, 95% CI 2.7 to 5.5, NNT 2) and other types of diclofenac plaster (RR 1.6, 95% CI 1.4 to 1.8, NNT 4).[3] In chronic musculoskeletal pain (mainly hand and knee OA), NSAID therapies included topical diclofenac and ketoprofen for 6 to 12 weeks.[12] Evidence was analyzed as moderate to high-quality for the chronic pain assessments.[3] Various formulations of diclofenac reduced pain compared to placebo for durations less than 6 weeks (RR 1.9, 95% CI 1.5 to 2.3, NNT 5) and for durations greater than 6 weeks (RR 1.2, 95% CI 1.1 to 1.3, NNT 10).[3] In PHN, topical high-concentration capsaicin had moderate-quality evidence of efficacy in reducing pain compared to placebo (RR 1.3, 95% CI 1.0 to 1.7, NNT 11).[3]

Evidence of efficacy for topical salicylate in acute and chronic pain was low quality.[3] There were quality and potential bias issues, and the available data did not show good evidence of effect, or showed no effect. Evidence of efficacy for low-concentration capsaicin (0.075%) and topical lidocaine in treatment of neuropathic pain was very low quality and typically limited to single studies or comparisons with sparse data.[3] Few analyses were possible due to poor reporting and only a single study with 58 participants provided relevant data for topical lidocaine efficacy.[3] Insufficient evidence was noted for topical capsaicin 0.04% in

PHN.[3] There were 124 participants in two studies.[3] Pooled analysis found no difference in efficacy between capsaicin and placebo.[3] No specific GRADE assessment was made for the 2 trials.[3]

In acute pain, systemic or local AE rates with topical NSAIDs (4.3%) were no greater than with topical placebo (4.6%) (RR 0.98, 95% CI 0.8 to 1.2, 42 studies, 6740 participants; high quality evidence).[3] Moderate-quality evidence indicated there were more local AEs in chronic pain conditions with topical diclofenac (14%) than placebo (8%) (RR 1.8, 95% CI 1.5 to 2.2, NNH 16).[3] Local pain with topical capsaicin 8% was more frequent (10%) than with placebo (4%) for neuropathic pain (RR 2.4, 95% CI 1.4 to 4.1, NNH 16; moderate-quality evidence).[3] In chronic pain, local AEs with topical capsaicin 0.04% (63%) were higher than topical placebo (24%) (RR 2.6, 95% CI 2.1 to 3.3, 5 studies, 557 participants, NNH 3; high-quality evidence).[3]

In chronic pain conditions, study withdrawals due to lack of efficacy were lower with topical diclofenac (6%) than placebo (9%) (RR=0.6, 95% CI 0.5 to 0.8, 11 studies, 3455 participants, moderate-quality evidence), and topical salicylate (2% vs 7% for placebo, RR 0.4, 95% CI 0.2 to 0.9, 5 studies, 501 participants, very low-quality evidence).[3] Study withdrawal due to an adverse event for treatment of chronic pain were higher with low-concentration topical capsaicin (15%) than placebo (3%) (RR 5.0, 95% CI 5.7 to 14, 4 studies, 477 participants, NNH 8; very low-quality evidence), topical salicylate (5% vs 1% for placebo, RR 4.2, 95% CI 1.5 to 12, 7 studies, 735 participants, NNH 26; very low-quality evidence), and topical diclofenac (5% vs 4% for placebo, RR 1.6, 95% CI 1.1 to 2.1, 12 studies, 3552 participants, NNH 51; very low-quality evidence).[3]

In summary, there is good evidence that formulations of topical diclofenac are useful in acute pain conditions such as sprains or strains.[3] In chronic musculoskeletal conditions with assessments over 6 to 12 weeks, topical diclofenac had limited efficacy in hand and knee OA, as did topical high-concentration capsaicin in management of PHN.[3] Efficacy of topical salicylate, low-concentration capsaicin, and lidocaine are not well supported by evidence, and have limited evidence of effect in reducing pain associated with acute or chronic pain conditions.[3]

Cochrane: Topical Non-steroidal Anti-Inflammatory Drugs for Acute Musculoskeletal Pain in Adults

A 2019 Cochrane review updated a 2010 systematic review focused on evaluating the safety and efficacy of topical NSAIDs in relieving acute pain in adults.[4] Literature was searched through February 2015 with a focus on use of NSAIDS in acute musculoskeletal pain. Formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin were studied. Criteria included randomized, controlled, double-blind studies comparing topical NSAIDs with placebo (inert carrier) or other active treatment for acute pain, with at least 10 participants per treatment arm and outcomes assessed at a minimum of 3 days).[4] Most studies enrolled participants who had sprains, strains, and contusions, usually as a result of sports injuries, but there was a wide range of when treatment was started from time of injury, from within a few hours to days.[4] Other studies enrolled participants with overuse-type injuries, such as tendinitis and acute low back pain, where pain had been present for days or weeks, but less than 3 months.[4] Fourteen new studies met inclusion criteria.[4] Most of the new trials compared diclofenac formulations with placebo. The primary outcome was clinical success, defined as either at least a 50% reduction in pain or an equivalent measure, such as a very good or excellent global assessment of treatment, or none to slight pain on rest or movement, measured on a categorical scale.[4] Numbers of participants with AEs and withdrawals due to AEs were analyzed as secondary outcomes. A total of 58 studies were included in the meta-analysis.[4] Most of the trials were of low to moderate risk of bias. Twenty-seven studies were at high risk of bias due to small population size (less than 50 participants in the treatment arm).[4]

Ten studies (n=2050) compared diclofenac with placebo.[4] The proportion of participants experiencing successful treatment with topical diclofenac was 74% compared to 47% of placebo treated participants (RR 1.6 95% CI 1.5 to 1.7, NNT 4).[4] Fifteen studies (n=3271) provided adequate data to analyze local AEs with

diclofenac. Similar AE rates were reported by 3.1% of patients who used topical diclofenac compared with 4.3% of patients who were in the placebo arm (RR 0.78, 95% CI 0.56 to 1.1).[4]

Thirty-six studies (n=5576) contributed data on systemic adverse events for all topical NSAIDs. There was no statistically significant difference between treatment groups in the proportion of patients who experienced an adverse event (topical NSAIDs 3.1% vs. placebo 3.5%, RR 0.96, 95% CI 0.73 to 1.3).[4] Forty-two studies (n=6405) reported adverse event withdrawal data. There was no statistically significant difference between treatment groups with respect to withdrawals due to AEs (topical NSAIDs 0.98% vs. placebo 0.99%, RR 1.0, 95% CI 0.64 to 1.6).[4]

Safety of Topical Non-steroidal Anti-Inflammatory Drugs in Osteoarthritis

A 2019 systematic review assessed the safety of topical NSAIDs in the management of OA in a meta-analysis of placebo-controlled RCTs.[5] A comprehensive literature search was undertaken through August 2017.[5] The primary outcomes were overall severe and serious AEs, as well as the following organ-related AEs: GI, vascular, cardiac, nervous system, skin and subcutaneous tissue, musculoskeletal, and connective tissue. Twenty-five RCTs were included in the qualitative synthesis and 19 were included in the meta-analysis: 8 RCTs of diclofenac, 4 RCTs of ketoprofen, 3 RCTs of ibuprofen, and 1 RCT each on eltenac, piroxicam, nimesulide and S-flurbiprofen.[5] Most of the trials included patients with knee OA; only two trials were conducted in patients with hand OA, and one study included patients with lumbar OA.[5] Trial durations varied between 1 and 12 weeks. All topical NSAIDs were assessed as high-quality for each outcome based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[5]

Eight studies with low risk of bias compared topical diclofenac with placebo.[5] Overall, there was a significant increase in total AEs with topical diclofenac compared with placebo (OR 1.30, 95% CI 1.10 to 1.53; high-quality evidence).[5] The rate of study withdrawals due to AEs was statistically significantly higher with topical diclofenac compared with placebo (OR 2.00, 95% CI 1.27 to 3.14; high-quality evidence).[5] High-quality evidence showed there was no statistically significant difference in odds for severe (OR 1.19, 95% CI 0.68 to 2.07) or serious AEs (OR 0.94, 95% CI 0.26 to 3.42), or for specific organ-related AEs, in patients treated with diclofenac compared with those who received placebo.[5] In particular, topical diclofenac was not associated with increased GI toxicity compared to placebo (OR 1.11, 95% CI 0.75 to 1.64; high-quality evidence).[5]

The use of topical NSAIDs was associated with a nearly 50% increase in study withdrawal due to an AE compared with placebo (OR 1.49, 95% CI 1.15 to 1.92; high-quality evidence).[5] Overall, more AEs (OR 1.16, 95% CI 1.04 to 1.29; high-quality evidence) were observed with topical NSAIDs compared with placebo.[5] Similar outcomes were found with topical diclofenac compared with placebo, largely driven by an increase in skin and subcutaneous tissue disorders (OR 1.73, 95% CI 0.96 to 3.10), but the difference was not statistically significant.[5]

Topical Anesthetics

Cochrane: Topical Agents for Pain in Venous Leg Ulcers

A 2012 Cochrane systematic review examined the evidence of EMLA cream prior to ulcer debridement from 6 placebo-controlled RCTs involving 343 participants with leg ulcer pain.[7] Participants who received EMLA cream had statistically significantly lower pain ratings on a 0 to 100 mm visual analog scale (VAS) (mean difference, -20.65 mm; 95% CI -12.19 to -29.11 mm; $p < 0.00001$) during ulcer debridement.[7] No statistically significant between group differences in burning or itching were observed.[7] Overall quality of evidence from these studies was rated as moderate.[7] All 6 RCTs were sponsored by Astra Zeneca.

Cochrane: Topical Anesthetics for Pain Control During Repair of Dermal Laceration

A 2017 Cochrane review updated a previously published 2011 report focused on the safety and efficacy of topical anesthetics for pain control during repair of dermal laceration.[8] The following objectives were analyzed: whether benefits of non-invasive topical anesthetic application occur at the expense of decreased analgesic efficacy, a comparison of the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal laceration, and to determine the clinical necessity for topical application of cocaine used as a therapeutic anesthetic.[8] The literature search was conducted through December 2016. Randomized controlled trials that evaluated the efficacy and safety of topical anesthetics for repair of dermal laceration in adult and pediatric patients were included. Topical anesthetics included bupivacaine, lidocaine, EMLA, lidocaine-epinephrine-tetracaine (LET), prilocaine, and tetracaine.[8] Two new studies were identified, which resulted in a final analysis of 25 RCTs involving 3,278 participants.[8] Most trials were at high risk of bias due to inadequate blinding, unclear concealment of allocation, and small sample sizes.[8] Local anesthetic efficacy during procedures such as wound repair was assessed by the patient's self-report of pain intensity during the intervention.[8] Acceptable tools for quantifying pain intensity included the VAS, the numerical rating scale, and a verbal rating scale.[8]

There was insufficient evidence to compare efficacy of topical anesthetics versus infiltrated local anesthesia.[8] The second objective, to compare the efficacy of various single-component or multi-component topical anesthetic agents for repair of dermal lacerations, found no significant differences between formulations, but the available data had high risk of bias.[8] For the final objective, researchers found that several cocaine-free topical anesthetics provided effective analgesic efficacy.[8] However, data regarding the efficacy of each topical agent are based mostly on single comparisons in trials with unclear or high risk of bias.[8]

The overall quality of the evidence according to the GRADE system is low, owing to limitations in design and implementation, imprecision of results, and high probability of publication bias (selective reporting of data).[8] Additional well-designed RCTs with low risk of bias are necessary before definitive conclusions can be reached.[8]

After review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[25-29] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[30-32]

New Guidelines:

American College of Rheumatology/Arthritis Foundation

The ACR/AF 2019 guideline on management of hand, hip, and knee OA updated their 2012 recommendations.[6] This guideline used the GRADE methodology to rate the quality of the available evidence and to develop recommendations.[6] An interprofessional voting panel included rheumatologists, an internist, physical and occupational therapists, and patients.[6] Literature published through August 2018 was used in the evidence review. Pertinent recommendations for topical analgesics are summarized in the three statements below:

- Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.[6]

In keeping with the principle that medications with the least systemic exposure (i.e., local therapy) are preferable, topical NSAIDs should be considered prior to use of oral NSAIDs. Practical considerations (e.g., frequent hand washing) and the lack of direct evidence of efficacy in the hand lead to a conditional recommendation for use of topical NSAIDs in hand OA.[6] In hip OA, the depth of the joint beneath the skin surface suggests that topical NSAIDs are unlikely to confer benefit, and thus, the voting panel did not examine use in hip OA.[6]

- Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended *against* in patients with hand OA.[6]

Topical capsaicin is conditionally recommended for treatment of knee OA due to small effect sizes and wide confidence intervals in the available literature.[6] Topical capsaicin in hand OA is not recommended because of a lack of direct evidence to support use, as well as increased risk of contamination of the eye when

applied to the hand.[6] In hip OA, the depth of the joint beneath the skin surface suggests that topical capsaicin is unlikely to have a meaningful effect, and thus, the voting panel did not examine use of topical capsaicin in hip OA.[6]

- Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.[6]

New Formulations or Indications:

- In March 2019, Flector® (diclofenac epolamine) topical system received an expanded indication for treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years of age and older.[33] Prior to this change, the Flector® labeling did not state if use in pediatric patients was appropriate.

- In February 2020, the FDA approved Voltaren® (diclofenac) 1% topical gel to be available over-the-counter (OTC) through the FDA's prescription-to-OTC switch process.[34] This process is usually initiated by the manufacturer of the prescription drug. For a drug to switch to nonprescription status, the manufacturer must show that consumers can understand how to use the drug safely and effectively without the supervision of a healthcare professional.[34] The OTC product will be called Voltaren Arthritis Pain and is indicated for the temporary relief of OA pain.[34]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts[35]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Benzocaine	Anbesol, Orabase, Orajel, Baby Orajel, Hurricaine, and Topex	May 2018	Warnings and Contraindications	Over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. Benzocaine oral drug products should only be used in adults and children 2 years and older if they contain certain warnings on the drug label. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Due to the significant safety risk of methemoglobinemia, manufacturers are urged to stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years.
Topical Lidocaine and Topical Lidocaine in combination with Prilocaine or Tetracaine	Lidoderm, Oraquix, Pliaglis, Synera, Xylocaine, Zingo	November 2018	Warnings and Precautions	Risk of Methemoglobinemia added to Prescribing Information Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with G6PD deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary

				compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended. Signs and symptoms of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine patch 5% and any other oxidizing agents. Depending on the severity of the symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. More severe symptoms may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Randomized Controlled Trials:

A total of 23 citations were manually reviewed from the initial literature search. After further review, 22 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 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Diwan et al[36] OL,RCT n=20	1. Transdermal diclofenac 200 mg patch x 1 for 24 hours 2. Diclofenac SR 100 mg BID x 2 doses over 24 hours	Adults aged 20-50 years with chronic periodontitis requiring flap operation	Pain as assessed by a VAS with 6 points (no pain, slight, mild, moderate, severe, horrible) and PIS with 5 points (no pain, very mild pain, mild pain, moderate pain, severe pain) were used to assess the pain 24 hours post-procedure	Minimum / Maximum / Mean / P-value VAS-Transdermal 0.0 / 1.0 / 0.6±0.51 / 0.48 VAS -Oral 0.0 / 1.0 / 0.8±0.42 PIS-Transdermal 0.0 / 2.0 / 1.2±0.63 / 0.16 PIS- Oral 0.0 / 2.0 / 1.6±0.8 There was no statistically significant difference in pain reduction between transdermal patch group and oral diclofenac group for either VAS or PIS assessments

<table>
<tr>
<td>Cozzi et al[37]

MC, RCT

n=356</td>
<td>1. Warm lidocaine and tetracaine patch 30 minutes before needle procedure

2. Lidocaine and prilocaine (EMLA) cream 60 minutes before needle procedure</td>
<td>Pediatric patients aged 3 to 10 years who needed venipuncture or IV cannulation</td>
<td>The primary outcome of this study was the success rate in performing venipuncture or intravenous cannulation at the first attempt.

Secondary outcomes included the procedural pain score, which was self-reported by children.</td>
<td>Main Study Outcomes
<table>
<tr><th>Outcome</th><th>Lidocaine/ Tetracaine Patch</th><th>EMLA</th><th>RR (95% CI) and p-value</th></tr>
<tr><td>Procedural Success [n (%)]</td><td>158 (92.4%)</td><td>142 (85.0%)</td><td>1.09 (1.01 to 1.17) p=0.03 NNT=14</td></tr>
<tr><td>Pain Score > 4 [n (%)]</td><td>18 (10.5%)</td><td>15 (9.0%)</td><td>1.17 (0.61 to 2.24) p=0.65</td></tr>
</table>
Warm lidocaine and tetracaine patch and EMLA cream provided equally useful pain relief</td>
</tr>
<tr>
<td colspan="5">Abbreviations: BID = twice daily; CI = confidence interval; EMLA = eutectic mixture of local anesthetics; IV = intravenous; MC = multi-center; mg = milligram; n = number; NNT = number needed to treat; OL=open-label; PIS = pain intensity scale; RCT = randomized clinical trial; RR = relative risk; SR = sustained release; VAS = visual analog scale</td>
</tr>
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Appendix 1: Current Preferred Drug List

Topical Analgesics

Generic	Brand	Form	Route	PDL
capsaicin	ARTHRITIS PAIN RELIEVING	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN-HP	CREAM (G)	TOPICAL	Y
capsaicin	HIGH POTENCY CAPSAICIN	CREAM (G)	TOPICAL	Y
capsaicin	CAPSAICIN	LOTION	TOPICAL	N
capsaicin	ZOSTRIX	STICK (EA)	TOPICAL	N
capsaicin/me-salicylate/menth	ZIKS	CREAM (G)	TOPICAL	N
capsaicin/skin cleanser	QUTENZA	KIT	TOPICAL	N
diclofenac epolamine	DICLOFENAC EPOLAMINE	PATCH TD12	TRANSDERM	N
diclofenac epolamine	FLECTOR	PATCH TD12	TRANSDERM	N
diclofenac epolamine	LICART	PATCH TD24	TRANSDERM	N
diclofenac sodium	DICLOFENAC SODIUM	DROPS	TOPICAL	N
diclofenac sodium	KLOFENSAID II	DROPS	TOPICAL	N
diclofenac sodium	DICLOFENAC SODIUM	GEL (GRAM)	TOPICAL	N
diclofenac sodium	VOLTAREN	GEL (GRAM)	TOPICAL	N
diclofenac sodium	PENNSAID	SOL MD PMP	TOPICAL	N
diclofenac sodium	PENNSAID	SOLN PK(G)	TOPICAL	N

diclofenac/kinesiology tape	XRYLIX	KIT	TOPICAL	N
lidocaine	LIDOCAINE	ADH. PATCH	TOPICAL	N
lidocaine	LIDODERM	ADH. PATCH	TOPICAL	N
lidocaine	ZTLIDO	ADH. PATCH	TOPICAL	N
lidocaine	LIDOCAINE	OINT. (G)	TOPICAL	N
lidocaine/kinesiology tape	LIDOPURE PATCH	COMBO. PKG	TOPICAL	N
cocaine HCl	COCAINE HCL	SOLUTION	TOPICAL	
diclofenac/capsicum oleoresin	DERMACINRX LEXITRAL	CMB SOL CR	TOPICAL	
diclofenac/capsicum oleoresin	DICLOFEX DC	CMB SOL CR	TOPICAL	
hydrocortisone/pramoxine	EPIFOAM	FOAM	TOPICAL	
lidocaine HCl	LIDOCAINE HCL	CREAM (G)	TOPICAL	
lidocaine HCl	LIDOTRAL	CREAM (G)	TOPICAL	
lidocaine HCl	GLYDO	JEL/PF APP	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	JEL/PF APP	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	JELLY(ML)	MUCOUS MEM	
lidocaine HCl	LIDOZION	LOTION	TOPICAL	
lidocaine HCl	LIDOCAINE HCL	SOLUTION	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL VISCOUS	SOLUTION	MUCOUS MEM	
lidocaine HCl	LIDOCAINE HCL	SOLUTION	TOPICAL	
lidocaine HCl	PRE-ATTACHED LTA KIT	SOLUTION	TOPICAL	
lidocaine/dimethicone	DERMACINRX ZRM PAK	KIT PAT-CR	TOPICAL	
lidocaine/emollient cmb no.102	DERMACINRX PHN PAK	KIT PAT-CR	TOPICAL	
lidocaine/hydrocortisone ac	LIDOCAINE-HYDROCORTISONE	CREAM (G)	TOPICAL	
lidocaine/priloc/lidocaine HCl	PRIZOTRAL	CREAM (G)	TOPICAL	
lidocaine/priloc/lidocaine HCl	PRIZOTRAL-II	CREAM (G)	TOPICAL	
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	CREAM (G)	TOPICAL	
lidocaine/prilocaine	APRIZIO PAK	KIT	TOPICAL	
lidocaine/prilocaine	DERMACINRX EMPRICAINE	KIT	TOPICAL	
lidocaine/prilocaine	DERMACINRX PRIZOPAK	KIT	TOPICAL	
lidocaine/prilocaine	EMPRICAINE-II	KIT	TOPICAL	
lidocaine/prilocaine	LIDOCAINE-PRILOCAINE	KIT	TOPICAL	
lidocaine/prilocaine	PRILO PATCH	KIT PAT-CR	TOPICAL	
lidocaine/prilocaine/silicone	NUVAKAAN	KIT	TOPICAL	
lidocaine/prilocaine/silicone	NUVAKAAN-II	KIT	TOPICAL	
lidocaine/silicone, adhesive	ZILACAINE PATCH	COMBO. PKG	TOPICAL	
lidocaine/tetracaine	PLIAGLIS	CREAM (G)	TOPICAL	
lidocaine/tetracaine	SYNERA	M.HT PATCH	TOPICAL	

Appendix 2: Abstracts of Comparative Clinical Trials

1. **A comparative evaluation of transdermal diclofenac patch with oral diclofenac sodium as an analgesic drug following periodontal flap surgery: A randomized controlled clinical study.**[36]

Diwan V, Srinivasa TS, Ramreddy KY, Agrawal V, Nagdeve S, Parvez H

BACKGROUND: Pain is an inevitable outcome of any periodontal surgery. Controlling postoperative pain is of utmost importance so as to increase patient compliance. The present study aims to compare the degree of postoperative analgesia with the use of oral diclofenac sodium and transdermal diclofenac patch following periodontal flap surgery in patients with chronic periodontitis.

MATERIALS AND METHODS: A total of 20 patients requiring full mouth flap surgery were selected for this study. Flap surgery was performed quadrant-wise and transdermal diclofenac patch was applied on the right arm following surgery of one of the quadrants and 100 mg oral diclofenac sodium twice daily was prescribed following surgery of the subsequent quadrant. The postoperative pain was recorded on visual analog scale and pain intensity scale 24 h after the surgery.

RESULTS: Both the statistical and clinical observation showed that diclofenac sodium administered transdermally has equal efficacy as compared to drug administered orally.

CONCLUSION: The study concludes that the diclofenac administered transdermally has equal potency in relieving postoperative pain as compared to orally administered diclofenac sodium following modified flap surgery. Transdermal patch has an added advantage of better patient compliance as it does not cause gastric disturbance.

2. **First-time success with needle procedures was higher with a warm lidocaine and tetracaine patch than an eutectic mixture of lidocaine and prilocaine cream.**[37]

Cozzi, G., Borrometi F, Benini F, et al.

Aim: More than 50% of children report apian during venipuncture or intravenous cannulation and using local anesthetics before needle procedures can lead to different success rates. This study examined how many needle procedures were successful at the first attempt when children received either a warm lidocaine and tetracaine patch or an eutectic mixture of lidocaine and prilocaine (EMLA) cream.

Methods: We conducted this multicenter randomized controlled trial at three tertiary-level children's hospitals in Italy in 2015. Children aged three to 10 years were enrolled in an emergency department, pediatric day hospital and pediatric ward and randomly allocated to receive a warm lidocaine and tetracaine patch or EMLA cream. The primary outcome was the success rate at the first attempt.

Results: The analysis included 172 children who received a warm lidocaine and tetracaine patch and 167 who received an EMLA cream. The needle procedure was successful at the first attempt in 158 children (92.4%) who received the warm patch and in 142 children (85.0%) who received the cream ($p = 0.03$). The pain scores were similar in both groups.

Conclusion: This study showed that the first-time needle procedure success was 7.4% higher in children receiving a warm lidocaine and tetracaine patch than EMLA cream.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 1 2020, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 17, 2020.

1.	Benzocaine/	1145
2.	Pramoxine.mp	60
3.	Prilocaine/or Lidocaine, Prilocaine Combinations	2140
4.	Tetracaine	2601
5.	Capsaicin	10309
6.	Diclofenac	7748
7.	Capsicum/	3216
8.	Methyl salicylate.mp	1102
9.	Lidocaine	24233
10.	Cocaine	23944
11.	Analgesics	48017
12.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	96185
13.	Administration, Topical	38069
14.	12 and 13	2122
15.	Acute pain/ or Pain/	133987
16.	14 and 15	431
17.	limit 16 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	23

Lidocaine Patch

Goal(s):
- Provide coverage only for funded diagnoses that are supported by the medical literature.

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

Requires PA:
- Lidocaine Patch

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 4
4. Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days

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

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

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

P&T Review: *8/2020 (DM); 7/18 (DM); 3/17*
Implementation: *4/1/17*

Drug Use Research & Management Program
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Drug Class Update: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Date of Review: August 2020

Date of Last Review: May 2017
Dates of Literature Search: 05/01/2017 - 05/05/2020

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

Purpose for Class Update:
The purpose of this update is to evaluate new evidence for proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). Prior authorization (PA) criteria for PPIs will be reviewed to determine the need to clarify risk factors and appropriate treatment durations.

Research Questions:
1. What is the comparative effectiveness of PPIs in the treatment of peptic ulcer disease (PUD), gastrointestinal esophageal reflux disease (GERD), Zollinger-Ellison syndrome, *Helicobacter pylori (H. pylori)* eradication and non-steroidal anti-inflammatory drugs (NSAID)-induced ulcers?
2. What is the comparative effective evidence of H2RAs in the treatment of GERD?
3. What is the comparative safety of PPIs in the treatment of PUD, GERD, Zollinger-Ellison Syndrome, *H. pylori* eradication and NSAID-induced ulcers?
4. What is the comparative safety of H2RAs in the treatment of GERD?
5. What is the evidence is for the risk of gastrointestinal (GI) bleeding for aspirin, NSAIDs or anticoagulants?
6. What is the evidence for the optimal treatment duration with a PPI or H2RA?
7. Are there subpopulations in which a PPI or H2RA may be more effective or cause more harm?

Conclusions:
- One high quality guideline, two high quality systematic reviews and meta-analyses, one safety warning and one new product was identified for this drug class update.
- A high quality guideline from the National Institute for Health and Care Excellence (NICE) on the management of GERD supports current policy, including treatment durations on PPI and H2RA therapies.[1]
- In a Cochrane review of patients with functional dyspepsia, PPIs improved global symptoms of dyspepsia more than placebo (629 per 1000 patients versus 714 per 1000 patients; RR 0.88; 95% CI, 0.82 to 0.94/NNT 11 up to 8 weeks of therapy) (moderate quality evidence).[2] No difference in global symptoms of dyspepsia was demonstrated with the combination of PPIs and prokinetics (cisapride, mosapride [not available in the United States (US)]), itopride [not available in the US]) compared to prokinetics alone based on moderate evidence (RR 0.85; 95% CI, 0.68 to 1.08).[2]

Author: Kathy Sentena, PharmD

- The Food and Drug Administration has recommended that all formulations of ranitidine (ZANTAC) be removed from the market due to contaminates of N-Nitrosodimethylamine (NDMA), a carcinogen, in ranitidine products.[3]
- A new *H. pylori* triple therapy, TALICIA (omeprazole, amoxicillin and rifabutin), was approved in 2019.[4] Approval was based on one placebo-controlled trial and one active treatment trial comparing TALICIA to omeprazole and amoxicillin. There is low strength of evidence from 2 trials that TALICIA has higher eradication rates versus comparators.
- There is insufficient evidence to differentiate the need for PPI therapy to reduce the risk of GI bleeds between non-selective NSAIDs, aspirin and anticoagulants.
- There was insufficient evidence in subgroups or Medicaid-specific populations.

Recommendations:
- After clinical review no changes to the preferred drug list (PDL) are warranted.
- Modify PPI PA criteria to clarify durations of therapy.
- Review costs in the executive session.

Summary of Prior Reviews and Current Policy:
- Previous reviews have demonstrated no clinically significant differences in efficacy or safety between the PPIs. There is insufficient evidence of efficacy and safety differences between H2RAs.
- Coverage duration of PPI therapy for GERD is limited to 8 weeks based upon the Health Evidence Review Commission (HERC) funding of the Oregon Health Plan (OHP) prioritized list due to long-term safety concerns. PA criteria for H-pylori therapy is 2 weeks and other funded conditions for up to 1 year (**Appendix 4**).

Background:
There are many indications which necessitate the use of PPIs or H2RAs including PUD, GERD, Zollinger-Ellison syndrome, *H. pylori* eradication and NSAID-induced ulcers.[5] GERD is one of the most common GI conditions affecting one-third of adults.[6] Treatment recommendations for GERD depend upon the frequency and severity of symptoms. Eight weeks of low-dose H2RAs is recommended as initial treatment with escalation to a PPI for patients with severe symptoms or failure of twice-daily H2RAs.[7]

PPIs are the standard of care for the treatment of PUD, most often caused by the presence of *H. pylori* or NSAIDs.[8] Eradication of *H. pylori* is associated with higher healing rates of duodenal and gastric ulcers and should be treated if present.[8] First-line therapy for treatment of *H. pylori* should consider resistance patterns, prior exposure to antibiotics and patient allergies. First-line treatment options include triple therapy with clarithromycin, amoxicillin and a PPI or clarithromycin, metronidazole and a PPI. In most patients with a *H. pylori* diagnosis, a 14-day treatment of a PPI is sufficient, without maintenance therapy. Additional considerations in PUD management are the use of NSAIDs, recurrence and size of ulcer. Recommended treatment durations are presented in **Table 1.** Patients with persistent ulcers (presence of ulcers on repeat endoscopy, giant peptic ulcer [> 2 cm] and > 50 years or other comorbidities are present, history of frequent recurrent peptic ulcers [>2 documented per year], condition requiring long-term NSAID or aspirin use) and patients presenting with idiopathic ulcers (*H. pylori* negative, NSAID negative ulcer) may require maintenance PPI therapy. Patients with complicated ulcers (e.g., bleeding, perforation, penetration, or gastric outlet obstruction) may need treatment for up to 12 weeks.[8] Unless other risk factors are present, long-term prevention of a recurrent bleeding ulcer with additional antisecretory therapy is not recommended.[9] In patients with NSAID-induced ulcers, NSAID discontinuation is recommended. If an NSAID must be

used, then a cyclooxygenase-2 (COX-2)-selective NSAID, at the lowest effective dose, with a PPI is recommended. If a patient has low-dose aspirin-induced ulcer and they must continue therapy, then long-term concomitant PPI should also be given, regardless of aspirin dose.[10]

Table 1. Recommended Treatment Duration of PPI Therapy Based on Diagnosis[8,1]

Diagnosis	Duration of Therapy
Peptic Ulcer Disease (PUD)	4-8 weeks†
Duodenal Ulcer	4 weeks
Gastric Ulcer	8 weeks
H. pylori infection	14 days
Gastrointestinal Reflux Disease (GERD)	8 weeks*

Abbreviation: NSAID – non-steroidal anti-inflammatory drug

Key: * Coverage of PPI therapy for GERD is limited to 8 weeks for Fee-for-Service OHP patients. † Some patients with complicated peptic ulcer disease (ulcers with bleeding, perforation, penetration, or gastric outlet obstruction) may require up to 12 weeks of therapy.

Important treatment outcomes in the management of patients requiring treatment with PPIs and H2RAs are: healing of ulcers, reduction in symptoms of dyspepsia, eradication of *H. pylori* and quality of life.

Utilization for this class is not a substantial contributor to the overall prescription expenditures for the Oregon Health Authority (OHA). Preferred PPIs account for 90% of utilization in the Fee-for-Service (FFS) OHP population. Ninety-four percent of H2RAs are for preferred therapies.

Methods:

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

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

New Systematic Reviews:

Cochrane: Proton Pump Inhibitors for Functional Dyspepsia

A 2018 Cochrane review evaluated the evidence for PPI use in people with functional dyspepsia (FD) with a focus on symptom management and quality of life.[2] Functional dyspepsia was defined as persistent or recurrent epigastric pain in patients with normal upper GI findings and symptom duration for at least a month, Rome II or III criteria (diagnosis of FD based on symptoms) or American Gastrological Association criteria for dyspepsia (dyspepsia not correlating with another diagnosis). Comparisons were between PPIs, H2RAs or prokinetics. Twenty-seven trials (only 3 trials were in the United States [US] and 5 trials were in multiple

countries including the US) in patients at least 16 years of age were identified through a literature search up to May of 2017. Groups of low-dose and standard dosing of PPIs were combined since evidence suggests similar efficacy. Studies lasted from 2-8 weeks. The primary outcomes were global symptoms of dyspepsia or epigastric pain/discomfort.

Trials included in the analysis were found to be at low risk for selection, detection, reporting and publication bias. Global symptoms of dyspepsia (reporting no or minimal symptoms) were reduced with the administration of PPIs compared to placebo based on moderate-quality evidence (629 per 1000 patients versus 714 per 1000 patients, respectively; RR 0.88; 95% CI, 0.82 to 0.94/NNT 11 with up to 8 weeks of therapy).[2] There was no evidence of difference in quality of life between PPIs and placebo based on Psychological General Well-Being Index and SF-36 combined (standard mean difference [SMD] 0.01 (95% CI, 0.09 to 0.11). A small benefit, that was not statistically significant, in reduction of global symptoms of dyspepsia was reported for PPI therapy over H2RAs based on low quality of evidence (650 per 1000 patients versus 739 per 1000 patients, respectively; RR 0.88; 95% CI, 0.74 to 1.04).[2] A marginal benefit in reduction of global symptoms of dyspepsia with PPI therapy over prokinetics may exist, but evidence was of low quality (RR 0.89; 95% CI, 0.81 to 0.99/NNT 16 with treatment 2 to 4 weeks). No reduction in global symptoms of dyspepsia was found when PPIs and prokinetics were combined compared to prokinetics alone for the treatment of FD, based on moderate quality evidence (377 per 1000 patients versus 444 per 1000 patients, respectively; RR 0.85; 95% CI, 0.68 to 1.08).[2] *H. pylori* status did not change results of studied outcomes. Adverse reactions between PPIs and placebo were not statistically significantly different based on moderate quality evidence (RR 0.99; 95% CI, 0.73 to 1.33).[2] No statistically significant differences between PPIs and H2RAs for adverse events were found, based on moderate quality evidence (137 per 1000 patients vs. 144 per 1000 patients, respectively). No differences between adverse events were reported between prokinetics and PPIs based on moderate quality evidence, 113 per 1000 patients compared to 123 per 1000 patients, respectively (RR 1.09; 95% CI, 0.79 to 1.49).[2] Adverse events were decreased in patients receiving combination PPI and prokinetics compared to prokinetics alone, based on moderate quality evidence (132 per 1000 patients versus 220 per 1000 patients, respectively; RR 0.60; 95% CI, 0.39 to 0.93).

Cochrane: Pharmacological Interventions for Prevention and Treatment of Upper Gastrointestinal Bleeding in Newborn Infants

A Cochrane review evaluated pharmacological interventions studied in preterm and term neonates for the prevention of upper GI bleeding.[11] The following treatments were included: PPIs, H2RAs, antacids, sucralfate or bismuth salts. Eleven trials were included in the systematic review, which included studies published up to July of 2018. None of the identified studies were of high quality and none had a low risk of bias.[11]

Four trials evaluated H2RAs for the prevention of GI bleeding in infants in the neonatal intensive care unit. Incidence of GI bleeding was 110 per 1000 patients in those treated with an H2RA compared to 305 per 1000 patients treated in the control group (no treatment) based on moderate quality evidence (RR 0.36; 95% CI, 0.22 to 0.58).[11] No difference in mortality was found between the groups.

The treatment of infants with an upper GI bleed was studied in 7 trials using either an H2RA or PPI. There was only low or very low quality of evidence available for analysis, and therefore, no strong conclusions could be drawn.

After review, 15 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).[12–25]

New Guidelines:

NICE – 2019 Surveillance of Gastro-Esophageal Reflux Disease and Dyspepsia in Adults: Investigation and Management

National Institute for Health and Care Excellence (NICE) updated previous guidance on the management of GERD and dyspepsia in adult patients.[1] Pharmacotherapies included in the review were PPIs and H2RAs. There was limited new evidence to update long-term safety of PPIs and regimens for *H. pylori*. Evidence was not pooled due to limited number of studies. A majority of recommendations from the 2014 guideline remained unchanged (**Table 2**). For the treatment of GERD, PPI therapy of up to 8 weeks is recommended. Recommendations for the treatment of esophagitis are full-dose PPI therapy for 8 weeks. Severe esophagitis may require treatment of a standard dose PPI as maintenance therapy if symptoms persist. Peptic ulcer disease treatment ranges from 2-8 weeks based on underlying cause.[1]

Table 2. NICE Recommendations for GERD and Dyspepsia[1]

Indication	Recommendation
GERD	Full-dose PPI for 4-8 weeks Treat recurrence of symptoms with PPI at lowest dose possible to control symptoms
Severe Esophagitis	Full-dose PPI for 8 weeks
Persistent Severe Esophagitis	Full dose PPI as maintenance therapy
Peptic Ulcer Disease	PPI or H2RA therapy for 8 weeks and treat *H. pylori* if present (stop NSAID if applicable) PPI or H2RA therapy for *H. pylori* negative patients for 4 to 8 weeks
Dilation of a Esophageal Stricture	Long-term full-dose PPI therapy
Functional Dyspepsia	Low-dose PPI or H2RA for 4 weeks If symptoms continue or recur, recommend PPI or H2RA at lowest possible dose (avoid long-term therapy)
H. pylori	PPI, amoxicillin and clarithromycin or metronidazole for 7 days For penicillin allergic, recommend a PPI, clarithromycin and metronidazole for 7 days For penicillin allergic, with previous clarithromycin exposure, recommend PPI, bismuth, metronidazole and tetracycline for 7 days
H. pylori after failure of first-line treatment	PPI, amoxicillin, clarithromycin or metronidazole (whichever has not been used previously) for 7 days PPI, amoxicillin and tetracycline if patient has had previous clarithromycin and metronidazole exposure for 7 days For penicillin allergic, recommend PPI, metronidazole and levofloxacin (if not previously used) for 7 days For penicillin allergic, with previous fluoroquinolone use offer a PPI, bismuth, metronidazole, and tetracycline
Children and Young People with persistent heartburn, retrosternal or epigastric pain	PPI or H2RA for 4 weeks
Infants	PPI or H2RA for 4 weeks for overt regurgitation and at least 1 of the following: unexplained feeding difficulties (for example, refusing feeds, gagging or choking), distressed behavior and faltering growth

Abbreviations: GERD – gastrointestinal reflux disease; H2RA - histamine-2 receptor antagonist; PPI – proton pump inhibitor

There was new high quality evidence supporting the efficacy of PPIs and H2RAs from 2 new systematic reviews and meta-analyses. A review which pooled results from PPIs, H2RAs and prostaglandins (termed "gastroprotectant" drugs) demonstrated prevention and healing of ulcers and upper GI bleeding.[1] There was no significant reduction in mortality (OR 0.85; 95% CI, 0.69 to 1.04; p=0.11).[1] Symptom recurrence after initial treatment should be treated with a PPI or H2RA at the lowest possible dose.

An update to the guidance on the treatment of *H. pylori* was made to consider levofloxacin as the fluoroquinolone of choice, but reserve fluoroquinolone use for when other antibacterial treatments cannot be used:[1]

- First-line option in patients allergic to penicillin and previous exposure to both clarithromycin and metronidazole
- Second-line option in patients with previous exposure to both clarithromycin and metronidazole
- Second-line treatment in patients who are allergic to penicillin and have not had a previous exposure to a fluoroquinolone

After further review, 4 guidelines were excluded due to poor quality.[26–29,30]

New Formulations or Indications:

TALICIA (omeprazole, amoxicillin and rifabutin): The 3-drug delayed release capsule combination product was approved in 2019 and indicated for the treatment of *H. pylori* infection in adults.[4] Each capsule contains 12.5 mg of rifabutin, 10 mg omeprazole and amoxicillin 250 mg. TALICIA is given as 4 capsules every 8 hours with food for 14 days. Approval was based on two trials. The first trial was a randomized, double-blind trial comparing TALICIA to a total daily dose combination of amoxicillin 3000 mg and omeprazole 120 mg in patients testing positive for *H. pylori.* Eradication rates were 83.8% in patients treated with TALICIA and 57.7% in the control group (amoxicillin and omeprazole) (P<0.0001).[4] A second double-blind, randomized, placebo-controlled trial reported eradication rates of 76.6% with TALICIA compared to 2.4% treated with placebo.[4]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ranitidine[3]	ZANTAC	April 2020	Contaminates of N-Nitrosodimethylamine (NDMA), a carcinogen, in ranitidine products	Removal of all ranitidine products from the market

Randomized Controlled Trials:

A total of 66 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Histamine-2 Receptor Antagonists

Generic	Brand	Form	PDL
famotidine	ACID CONTROLLER	TABLET	Y
famotidine	ACID REDUCER	TABLET	Y
famotidine	FAMOTIDINE	TABLET	Y
famotidine	HEARTBURN RELIEF	TABLET	Y
famotidine	PEPCID	TABLET	Y
ranitidine HCl	RANITIDINE HCL	SYRUP	Y
ranitidine HCl	ZANTAC	SYRUP	Y
ranitidine HCl	ACID CONTROL	TABLET	Y
ranitidine HCl	ACID REDUCER	TABLET	Y
ranitidine HCl	HEARTBURN RELIEF 150	TABLET	Y
ranitidine HCl	RANITIDINE	TABLET	Y
ranitidine HCl	RANITIDINE HCL	TABLET	Y
ranitidine HCl	ZANTAC	TABLET	Y
cimetidine	ACID REDUCER	TABLET	N
cimetidine	CIMETIDINE	TABLET	N
cimetidine	HEARTBURN RELIEF	TABLET	N
cimetidine	TAGAMET	TABLET	N
cimetidine HCl	CIMETIDINE	SOLUTION	N
cimetidine HCl	CIMETIDINE HCL	SOLUTION	N

famotidine	FAMOTIDINE	ORAL SUSP	N
famotidine	PEPCID RPD	TAB RAPDIS	N
famotidine/Ca carb/mag hydrox	ACID REDUCER COMPLETE	TAB CHEW	N
famotidine/Ca carb/mag hydrox	COMPLETE	TAB CHEW	N
famotidine/Ca carb/mag hydrox	DUAL ACTION COMPLETE	TAB CHEW	N
nizatidine	NIZATIDINE	CAPSULE	N
nizatidine	NIZATIDINE	SOLUTION	N
ranitidine HCl	RANITIDINE HCL	CAPSULE	N

Proton Pump Inhibitors

Generic	Brand	Form	PDL
omeprazole	OMEPRAZOLE	CAPSULE DR	Y
pantoprazole sodium	PANTOPRAZOLE SODIUM	TABLET DR	Y
pantoprazole sodium	PROTONIX	TABLET DR	Y
dexlansoprazole	DEXILANT	CAP DR BP	N
esomeprazole mag/glycerin	ESOMEP-EZS	KIT CAP SP	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	CAPSULE DR	N
esomeprazole magnesium	HEARTBURN TREATMENT	CAPSULE DR	N
esomeprazole magnesium	NEXIUM	CAPSULE DR	N
esomeprazole magnesium	NEXIUM 24HR	CAPSULE DR	N
esomeprazole magnesium	ESOMEPRAZOLE MAGNESIUM	SUSPDR PKT	N
esomeprazole magnesium	NEXIUM	SUSPDR PKT	N
esomeprazole strontium	ESOMEPRAZOLE STRONTIUM	CAPSULE DR	N
lansoprazole	HEARTBURN TREATMENT 24 HOUR	CAPSULE DR	N
lansoprazole	LANSOPRAZOLE	CAPSULE DR	N
lansoprazole	PREVACID	CAPSULE DR	N
lansoprazole	PREVACID 24HR	CAPSULE DR	N
lansoprazole	LANSOPRAZOLE	TAB RAP DR	N
lansoprazole	PREVACID	TAB RAP DR	N
omeprazole	OMEPRAZOLE	TAB RAP DR	N
omeprazole	OMEPRAZOLE	TABLET DR	N
omeprazole magnesium	ACID REDUCER	CAPSULE DR	N
omeprazole magnesium	OMEPRAZOLE MAGNESIUM	CAPSULE DR	N
omeprazole magnesium	PRILOSEC	SUSPDR PKT	N
omeprazole/sodium bicarbonate	OMEPRAZOLE-SODIUM BICARBONATE	CAPSULE	N
omeprazole/sodium bicarbonate	ZEGERID	CAPSULE	N
omeprazole/sodium bicarbonate	OMEPRAZOLE-SODIUM BICARBONATE	PACKET	N
omeprazole/sodium bicarbonate	ZEGERID	PACKET	N
pantoprazole sodium	PROTONIX	GRANPKT DR	N
rabeprazole sodium	ACIPHEX SPRINKLE	CAP DR SPR	N

rabeprazole sodium	ACIPHEX	TABLET DR	N
rabeprazole sodium	RABEPRAZOLE SODIUM	TABLET DR	N

Antacids, H. Pylori

Generic	Brand	Form	PDL
omeprazole/amoxicill/rifabutin	TALICIA	CAP IR DR	N
bismuth/metronid/tetracycline	PYLERA	CAPSULE	N
lansoprazole/amoxiciln/clarith	LANSOPRAZOL-AMOXICIL-CLARITHRO	COMBO. PKG	N
omeprazole/clarith/amoxicillin	OMECLAMOX-PAK	COMBO. PKG	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 17, 2020

Search Strategy:

#	Searches	Results
1	omeprazole.mp. or Omeprazole/	11353
2	pantoprazole.mp. or Pantoprazole/	2034
3	dexlansoprazole.mp. or Dexlansoprazole/	132
4	esomeprazole.mp. or Esomeprazole/	1654
5	lansoprazole.mp. or Lansoprazole/	2917
6	rabeprazole.mp. or Rabeprazole/	1361
7	bismuth.mp. or Bismuth/	12213
8	famotidine.mp. or Famotidine/	2243
9	ranitidine.mp. or Ranitidine/	7110
10	cimetidine.mp. or Cimetidine/	12587
11	nizantidine.mp.	1
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	43450
13	limit 12 to (english language and humans)	22376
14	limit 13 to yr="2017 -Current"	1310
15	limit 14 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	66

Appendix 3: Key Inclusion Criteria

Population	Patients with an indication for gastric acid suppression
Intervention	Proton pump inhibitor and histamine receptor antagonist therapy
Comparator	Placebo or active treatment regimen
Outcomes	Dyspepsia, ulcer healing rates, erosive esophagitis healing rates, quality of life
Timing	Symptom onset
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 68 days' duration
- Non-preferred PPIs

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/
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a preferred PPI?	**Yes:** Go to #5	**No:** Go to #3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	**Yes:** Go to #4	**No:** Pass to RPh; deny, not funded by OHP.

4. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives.	**No:** Go to #5
5. Has the patient already received 68 days of PPI therapy for either of the following diagnoses: • Esophagitis or gastro-esophageal reflux disease with or without esophagitis (K20.0-K21.9); or • Current *H. pylori* infection?	**Yes:** Go to #8	**No:** Go to #6
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalization?	**Yes:** Approve for 1 year	**No:** Go to #7

7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant; ii. Aspirin (all doses) or non-selective NSAID; or iii. Oral corticosteroid	**Yes:** Approve for 1 year	**No:** Go to #8
8. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	**Yes:** Approve for recommended duration.	**No:** Pass to RPh. Deny; medical appropriateness or not funded by OHP Message: Patient may only receive 8 weeks of continuous PPI therapy. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

Table. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	Maximum Duration	Maximum Daily Dose
GERD: Esophageal reflux (K219) Esophagitis (K200-K210)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Dexlansoprazole Solu Tab 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection (B9681)	2 weeks	Dexlansoprazole 60 mg Dexlansoprazole 30 mg† Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg
Duodenal Ulcer (K260-K269)	4 weeks	
Gastric Ulcer (K250-K259)	8 weeks	
Peptic ulcer site unspecified (K270-K279)	12 weeks	
Achalasia and cardiospasm (K220) Barrett's esophagus (K22.70; K22.71x) Dyskinesia of esophagus (K224) Esophageal hemorrhage (K228) Gastritis and duodenitis (K2900-K2901; K5281) Gastroesophageal laceration-hemorrhage syndrome (K226) Gastrojejunal ulcer (K280-K289) Malignant mast cell tumors (C962) Multiple endocrine neoplasia [MEN] type I (E3121) Neoplasm of uncertain behavior of other and unspecified endocrine glands (D440; D442; D449) Perforation of Esophagus (K223) Stricture & Stenosis of Esophagus (K222) Zollinger-Ellison (E164)	1 year	

*A current list of funded conditions is available at: https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx

† Dexlansoprazole SoluTab 30 mg (given as 2 SoluTabs at once) are not recommended for healing of erosive esophagitis.

Implementation: *6/8/16; 2/16; 10/15; 7/15; 4/15; 5/13; 5/12; 1/11; 4/10; 1/10; 9/06, 7/06, 10/04, 3/04*